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PANCREATITIS

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I. A STUDY OF 179 FATAL CASES

IN A broad sense pancreatitis includes all inflammations of the pancreas without regard to etiology, but this discussion is limited to inflammations resulting from escape of the pancreatic secretion into the parenchyma of the gland.

We have no cases in our necropsy service of pancreatitis due to mumps[15, 21] or other systemic infections. There are several examples of suppurative pancreatitis due to extension of an ulcer or carcinoma of the stomach or an empyema. Suppuration was sometimes found also in association with a primary carcinoma. All secondary forms of pancreatitis are omitted in this discussion.

At necropsy one occasionally finds small areas of fat necrosis in and about the pancreas in subjects that exhibited no symptoms of pancreatic disease. These no doubt represent mild pancreatitis, but this paper is limited to cases in which pancreatitis was the immediate cause of death.

From a clinical standpoint pancreatitis is best classified as acute and chronic. These two forms are basically the same disease and the separation between them is indefinite. I have arbitrarily classified as acute all cases in which the patient lived less than 3 months after the onset of the first acute attack. All cases of over 3 months' duration are classified as chronic. The term "recurrent" may be applied to those who have more than one acute attack; but some cases of short duration have more than one acute exacerbation, and many chronic cases exhibit no acute episodes.

Incidence.—The incidence of fatal pancreatitis in the necropsy population is shown in Table I. The incidence in men over 20 years of age is 0.25 per cent, and in women 0.36 per cent. In men 74 per cent and in women 84 per cent occur between the ages of 40 and 80 years. Based upon the percentage of deaths, the maximum incidence in men is in the third and fourth decades and in women

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in the fifth and sixth. Edmondson[16] found 62 cases among 33,500 necropsies—an incidence of 0.18 per cent; but his data were not analyzed with respect to age and sex. The clinical incidence of pancreatitis may be higher than these data suggest since many cases are mild and do not terminate fatally.

TABLE I. INCIDENCE OF FATAL PANCREATITIS IN NECROPSIES IN MEN AND WOMEN

AGE AT DEATH (YEARS)	NUMBER OF NECROPSIES	NUMBER OF CASES OF PANCREATITIS	PER CENT WITH PANCREATITIS
Men			
0 – 20	8,268	0	0.0
20 – 40	5,600	22	0.39
40 – 60	14,629	37	0.25
60 – 80	17,186	37	0.22
80 – 100	2,913	4	0.14
20 – 100	40,328	100	0.25
Women			
0 – 20	5,966	1	0.02
20 – 40	4,124	9	0.22
40 – 60	6,902	38	0.55
60 – 80	8,452	28	0.33
80 – 100	1,946	3	0.15
20 – 100	21,424	78	0.36

TABLE II. RELATIONSHIP OF CHOLELITHIASIS TO PANCREATITIS IN MEN AND WOMEN

	NECROPSIES			PANCREATITIS			
AGE	NUMBER OF NECROPSIES	NUMBER WITH CHOLELITHIASIS	PER CENT WITH CHOLELITHIASIS	NUMBER OF CASES	NUMBER WITH CHOLELITHIASIS	PER CENT WITH CHOLELITHIASIS	NUMBER WITH ALCOHOLISM
Men							
0 – 10	981	0	0.0	0	0	0.0	0
10 – 20	103	0	0.0	0	0	0.0	0
20 – 30	240	2	0.8	2	1	50.0	1
30 – 40	323	10	3.1	20	2	10.0	7
40 – 50	559	47	8.4	10	4	40.0	1
50 – 60	1,344	182	13.5	27	13	48.1	5
60 – 70	1,486	257	17.3	19	10	52.6	1
70 – 80	1,094	279	25.7	18	12	66.7	1
80 – 100	583	190	32.6	4	3	75.0	0
20 – 40	563	12	2.1	22	3	13.6	8
40 – 60	1,903	229	12.0	37	17	46.0	6
60 – 100	3,163	726	23.0	41	25	61.0	2
Women							
0 – 10	696	0	0.0	0	0	0.0	0
10 – 20	67	1	1.5	1	0	0.0	0
20 – 30	141	7	5.0	2	0	0.0	2
30 – 40	186	19	10.2	7	3	43.0	3
40 – 50	315	58	18.4	22	15	68.1	2
50 – 60	519	157	30.3	16	14	87.5	2
60 – 70	678	223	32.9	15	13	86.7	0
70 – 80	694	261	37.6	13	7	54.0	0
80 – 100	378	176	46.6	3	3	100.0	0
20 – 40	327	26	8.0	9	3	33.3	5
40 – 60	834	215	25.8	38	29	76.3	4
60 – 100	1,750	660	37.7	31	23	74.2	0

Age: The ages at death are shown in Table II. The ages of the 100 men ranged from 22 to 91 years and of the 79 women from 18 to 91 years. The

onset of symptoms was after the age of 40 years in 78 per cent. Some authors report a larger percentage under the age of 40 years.[19, 43, 46] This discrepancy is probably due to the type of clinical material studied. Alcoholic pancreatitis is more frequent in men and in the younger decades.

Sex: A few reports, dealing with relatively small groups and especially with alcoholic pancreatitis, indicate a great preponderance of men[19, 46]; but in large statistics women outnumber men.[18, 39, 43, 47, 52] The combined data from 14 clinical reports give 537 men and 768 women. This is approximately a ratio of 3 women to 2 men. Data from necropsies must be corrected for the preponderance of men. In our necropsies there are 100 men and 79 women, but the corrected ratio is roughly 3 women to 2 men (Table I). A similar sex distribution is found in Edmondson's necropsy statistics.[16]

Acute pancreatitis: The symptoms of acute pancreatitis vary with the severity of the attack. The diagnosis may be established by demonstrating an elevation of serum or urinary amylase in a patient with abdominal pain. A severe attack is accompanied by hyperglycemia and shock and often terminates fatally. The immediate mortality following the first acute attack varies from 10 to 30 per cent in different reports. Since this study is concerned only with fatal cases, the observations apply only to severe pancreatitis.

Of our 179 patients, 102 died during the first acute attack. There were 61 men and 41 women. The duration of life after onset was 0 to 7 days in 56, 8 to 14 days in 19, 15 to 21 days in 10, 22 days to 1 month in 8, and 1 to 3 months in 9 subjects. The symptoms persisted without interruption in 95 subjects, but in 7 cases with a duration of 1 to 3 months there was temporary improvement followed by an acute exacerbation. Some writers would classify these 7 cases as recurrent pancreatitis.

Chronic pancreatitis: This group includes 77 cases with a duration of over 3 months. There were 39 men and 38 women. Sixty-two patients had 2 or more acute attacks and may properly be called chronic recurrent pancreatitis; but in 15 subjects there were continuous abdominal symptoms without any acute exacerbations. This latter group is best designated as chronic pancreatitis. The duration of life after onset was as follows: 3 to 6 months, 10; 6 months to 1 year, 15; 1 to 2 years, 9; 2 to 3 years, 5; 3 to 5 years, 8; 5 to 10 years, 14; 10 to 15 years, 3; and indefinite duration, 13 patients. The onset is dated from the first attack of abdominal pain, but it is recognized that the first attack in some instances may have been gallstone colic and not pancreatitis. Thirty of the 39 cases with duration over one year had gallstones.

Pathology.—In fatal cases of acute pancreatitis the prominent macroscopic changes are enlargement of the pancreas, hemorrhage, fat necrosis and necrosis of the parenchyma, gangrene, and suppuration. In chronic pancreatitis the gross appearance is usually identical with that of the acute form, but often one finds areas of fibrosis and sometimes calcification or pseudocysts.

Hemorrhage was the most conspicuous gross alteration in about 50 per cent of the acute cases and 40 per cent of the chronic ones, and it was present in lesser degree in many others. Those who survived only a few days usually

showed hemorrhagic pancreatitis. Hemorrhage in chronic pancreatitis suggests a terminal acute exacerbation. After a few days the extravasated red cells undergo hemolysis and the red color disappears.

Fat necrosis is present in some degree in all cases and was the most conspicuous feature in 9 cases. It is caused by the lipase of the pancreatic secretion.

In 30 cases gangrene was a prominent feature. Usually those exhibiting gangrene were of longer duration than the average, but a few were of short duration. Suppuration is secondary to necrosis and is usually demonstrable microscopically in those who survive a few days.

In 9 chronic cases areas of fibrosis and atrophy were found within the pancreas. Calculi were found within the pancreatic ducts in 8 chronic cases, and in 2 others pseudocysts were observed. In 61 of the 77 chronic cases the pancreas could not be distinguished from acute pancreatitis.

Acute adematous pancreatitis is a well-established lesion aften observed at exploratory operation but seldom at autopsy. The clinical symptoms are less severe than those of the hemorrhagic and necrotizing types, and the patients usually recover. The pancreas is swollen and edematous and there are small areas of fat necrosis in and about the pancreas, but hemorrhage and parenchymal necrosis are not seen. There were 5 cases of this type among our 102 acute cases. The enlargement of the pancreas is due to interstitial edema. In clinical reports based upon exploratory operations this is the most frequent form of acute pancreatitis: Anglem,[1] 12 of 20; Rose[32] 48 of 89; Lewison,[31] 19 of 35; and McWhorter,[35] 18 of 64 cases. It is not known how often this type of pancreatitis progresses into the hemorrhagic and necrotizing types.

The Etiology of Pancreatitis.—The voluminous literature on this topic has recently been well reviewed by Richman[50] and others, and this discussion will therefore be restricted to a few phases of the problem. It is well established that pancreatitis is due to rupture of the small pancreatic ducts with escape of the pancreatic secretion into the parenchyma of the gland. The rupture is caused by increased intraductal pressure which is brought about by increased pancreatic secretion associated with some degree of obstruction to its outflow. Two diseases, namely, cholelithiasis and alcoholism, show a high correlation with pancreatitis.

Cholelithiasis: It has been known for many years that gallstones are found more frequently in association with pancreatitis than with other diseases. Statistics on the incidence of gallstones have little value unless analyzed with respect to age and sex since the percentage of persons with gallstones increases steadily with increasing age and is much higher in women than in men. Lieber[32] has shown also that gallstones are much less frequent in Negro than in white persons.

To study the relation of cholelithiasis to pancreatitis Table II has been constructed. The incidence of gallstones by decades is shown in 5,629 men and 2,911 women examined at necropsy in this department during the 4-year period from 1947 to 1951. The cases of pancreatitis include all that occurred during the

45-year period, 1911 through 1955. The frequency of cholelithiasis in the general necropsy population is compared with its incidence in subjects with pancreatitis.

The frequency of gallstones in necropsies increases in each decade and is about twice as high in women as in men up to the age of 70 years, after which the differences are less marked. The incidence of gallstones in our necropsies is definitely higher than in the large series reported by Ludlow,[33] Cleland,[10] and Lieber.[32] I have used our own necropsy statistics since the cases of pancreatitis are all from our necropsy service. The number of Negro persons is too small to affect the percentages appreciably.

A study of Table II brings out clearly that the incidence of gallstones in necropsies or in pancreatitis has little significance unless analyzed with respect to age and sex. Gallstones are very rare before the age of 20 years and are much less frequent in subjects 20 to 40 years of age than thereafter. If we subtract the expected incidence of gallstones from their actual incidence in pancreatitis in the age groups of each sex we may conclude that gallstones were an etiologic factor in pancreatitis in about one-third of the men over 40 years of age and about one-half of the women of corresponding age. Alcoholism is a more important influence than gallstones in pancreatitis in subjects under 40 years of age.

Collected statistics from the literature indicate that gallstones are associated with about one-half of the reported cases of pancreatitis,[27] but the data are not analyzed with respect to age or sex.

It seems well established that gallstones are in some way responsible for many cases of pancreatitis, perhaps one-third of those in men and one-half of those in women. The mechanism by which they induce pancreatitis, however, remains obscure. The mechanism described by Opie,[41, 42] namely, a stone lodged in the ampulla in such a position as to obstruct the pancreatic duct, is rarely seen at autopsy or operation. In our 179 cases of pancreatitis there were only 2 instances of ampullary stone. Stones were found in the common bile duct in 3 cases. Possibly the temporary lodgment of a stone may cause an increase of the intraductal pressure in the pancreas.

The frequency of pancreatitis in asymptomatic cholelithiasis is very low. In the necropsies listed in Table II there were 967 men with cholelithiasis of which only 8 had pancreatitis—an incidence of 0.8 per cent. Five of 902 women with cholelithiasis had pancreatitis—an incidence of 0.5 per cent. However, in 1,175 cases of symptomatic cholelithiasis, Rose[52] observed 35 cases of pancreatitis—about 3 per cent.

It is difficult to assess the role of symptomatic cholelithiasis in our 77 cases of chronic pancreatitis, since gallstone colic could not always be distinguished from pancreatitis on the history available. Five of the 77 chronic cases had a clinical diagnosis of cholelithiasis one or more years before death. Cholecystectomy appears to be justified in pancreatitis associated with gallstones.

Cholecystitis without stones is sometimes assigned as a cause of pancreatitis. However, cholecystitis is usually associated with stones; Sutton[61] found calculi

in 89.6 per cent of 513 operations for cholecystitis. Only one of our 179 cases of pancreatitis was associated with cholecystitis without stones.

The role of alcoholism in pancreatitis: An etiologic relationship between alcoholism and pancreatitis has been recognized for many years. The proportion of cases ascribed to alcoholism varies in different reports from 10 to 50 per cent. Ivy and Gibbs[27] in their survey found about 20 per cent attributed to alcoholism. Collected statistics from 15 authors[2, 3, 5, 11, 16, 19, 34, 35, 40, 43, 45, 48, 50, 54, 64] give 849 cases of pancreatitis of which 245, or about 29 per cent, were attributed to alcoholism. Twenty-five of our 179 patients with pancreatitis (14 per cent) were severe chronic alcoholics, and only one of this group had gallstones. It appears in Table II that 13 of the 25 patients were less than 40 years old. Of the 31 cases of pancreatitis in subjects less than 40 years of age, 6 were associated with gallstones and 13 with chronic alcoholism. Alcoholism is more important than cholelithiasis in the etiology of pancreatitis in subjects under 40 years of age.

Several authors report a high incidence of pancreatic lesions in subjects dead of acute or chronic alcoholism[9, 64]; but only a few of these lesions were severe. Culotta[12] observed a high serum amylase in 2 of 51 alcoholics without pancreatitis. Carter[8] studied 11 patients with the clinical signs of alcoholic gastritis. Edema of the pancreas was noted in 4 subjects who were explored, and a high serum amylase was found in 7 who were not operated upon. Dreiling[14] demonstrated that intravenous alcohol does not increase the volume of the pancreatic juice as oral alcohol does. It is believed that oral alcohol increases the output of secretin which stimulates the pancreas. Alcohol acts as a heavy meal does in that it increases the volume of the pancreatic juice. A number of patients with pancreatitis give a history of an attack following a heavy meal.

In alcoholic pancreatitis it is usually assumed that there is some form of obstruction to the free flow of the pancreatic juice but the nature of this obstruction, if it exists, is not known. Rich and Duff[48] suggested that metaplasia of the ductal epithelium is sufficient to cause obstruction. They found ductal metaplasia in 18.6 per cent of 150 consecutive necropsies and in 13 of 24 cases of hemorrhagic pancreatitis. The number of cases of pancreatitis studied is hardly sufficient to justify this conclusion. Yotuyanagi[66] found ductal metaplasia in 64 per cent of necropsies.

In a fairly large percentage of cases of pancreatitis no gallstones were present and the patient did not use alcohol excessively. For this group no etiology has been suggested.

Pancreatic lithiasis: Pancreatic lithiasis is usually a late manifestation of chronic recurrent pancreatitis. A majority of the reported cases are typical examples of this disease. Maimon[36] found calcification in 7 of 20 cases, Bartunek[2] in 7 of 19, and Comfort[11] in 14 of 29 cases of chronic recurrent pancreatitis. Comfort states that calcification develops in about one-third. Calcification is less frequent in my series, occurring in only 8 of 77 chronic cases. Five of my 8 cases were typical chronic recurrent pancreatitis, but 3 patients did not complain of abdominal pain. Calcification appears to develop more

frequently in men but no large series are available. Alcoholism plays a prominent role in the etiology, but gallstones are of only minor importance. Only one of my 8 cases was associated with cholelithiasis. Lithiasis differs from the usual form of chronic pancreatitis in that there is a greater destruction of pancreatic tissue and a higher incidence of diabetes and steatorrhea.

Calculi occlude the major and minor pancreatic ducts and thereby cause atrophy and fibrosis of the parenchyma. Sometimes the calcification is diffuse and not restricted to the ducts. The pancreas becomes small, hard, and fibrous. The acinar tissue is replaced by dense scar tissue, but often the islets persist and diabetes does not develop. Many patients with lithiasis do not give a history of pancreatitis (Gambill and Pugh[20]).

Outcome of Acute Pancreatitis.—The immediate mortality following an acute attack varies with its severity. Howard[26] reported 5 of 21 survivors of hemorrhagic pancreatitis, and 52 of 59 survivors from the nonhemorrhagic type. From other reports the immediate mortality was as follows: Raker,[47] 16 of 134; Richman,[50] 19 of 58; O'Brien,[40] 9 of 108; Siler,[58] 22 of 164; and Brinkman,[5] 4 of 25 patients.

In patients seen during an acute attack a history of one or more previous attacks was noted as follows: Paxton,[43] 187 of 307; McWhorter,[35] 42 of 64; Donhauser,[13] 66 of 86; and O'Brien,[40] 53 of 108. Sixty-two per cent of 565 cases of pancreatitis reported by these observers were of the recurrent type. Kaden[28] followed 100 survivors of acute pancreatitis for an average period of 3.5 years. Thirty-nine patients had one or more subsequent attacks. The recurrence rate in survivors of acute pancreatitis is apparently 40 to 60 per cent.

Experimental pancreatitis is fully discussed in the papers by Wangensteen[62] and Richman.[50] Experimental studies support the view that the major factors in pancreatitis are increased pancreatic secretion associated with some form of obstruction to its outflow.

II. THE RELATION OF PANCREATITIS TO DIABETES MELLITUS

Glycosuria.—A transient glycosuria in association with abdominal pain is evidence of pancreatitis. From a survey of the literature Schumacher[55] found glycosuria during the acute attack in 11 per cent. Donhauser[13] noted glycosuria in 28 of 86 patients. In our cases of pancreatitis, which were all severe, sugar was found in 35 of 102 subjects in which the urine was examined. Thus in two-thirds of these fatal cases, sugar was not found at the first examination. It was noted that glycosuria was often absent at first but present later. Sometimes a severe glycosuria persists from onset until death, and the patient has definite diabetes.

Hyperglycemia.—Hyperglycemia is found much more often than glycosuria and is probably present in some degree in all severe attacks of pancreatitis. It was found in 19 of our 21 cases in which the blood sugar was determined. Brocq and Varangot[6] in 72 cases found the blood sugar below 150 mg. per cent in 15, 150 to 200 in 23, and over 200 in 34 cases. Fallis[18] noted hyperglycemia in 44.6 per cent of 130 acute cases, and Donhauser[13] in 24 of 86. Sebening[56]

found an impaired glucose tolerance in each of 21 acute cases. After 6 months the tolerance was only slightly decreased, and after one year it had returned to normal.

Diabetes Following Pancreatitis.—If we define diabetes as hyperglycemia with glycosuria then all fatal cases of pancreatitis are diabetic at the time of death, and a transitory diabetes may be demonstrated during any severe attack of pancreatitis. If the patient survives the acute attack the signs of diabetes usually subside gradually, although an impaired glucose tolerance may often be demonstrated for several months. If the patient dies of pancreatitis several weeks after the onset of the acute attack, a typical picture of diabetes may develop. In 11 of my cases that survived from 10 days to 7 weeks, a typical picture of diabetes developed, and some were treated with insulin. The reports in the literature as to the frequency of diabetes following pancreatitis range from 2 to 30 per cent depending upon the type of pancreatitis studied and the concept as to what constitutes diabetes. Acute pancreatitis may be followed by a diabetes of short duration but rarely by a prolonged diabetes. Warren's[63] 5 cases of diabetes ranged in duration from 5 days to 4 months.

Schumacker[55] in 2,855 collected cases of acute pancreatitis found that less than 2 per cent developed diabetes. Chronic pancreatitis, however, frequently produces permanent diabetes. Diabetes is especially prone to develop in chronic pancreatitis with lithiasis.

The frequency of permanent diabetes following chronic pancreatitis is difficult to determine from the literature since many authors do not indicate whether the diabetes was of short or long duration. Combined statistics from 11 authors who were dealing with chronic pancreatitis, chiefly the form without calcification, give 36 cases of diabetes from 253 cases of chronic pancreatitis—an incidence of about 14 per cent.[2, 7, 11, 23-25, 34, 36, 52, 56, 57] In chronic pancreatitis with lithiasis, the incidence of diabetes is much greater. Combined data from 13 authors give 116 cases of diabetes among 255 cases of pancreatic lithiasis—an incidence of 45 per cent.[16, 17, 29, 30, 36-38, 44, 49, 51, 53, 59, 65]

In my 77 cases of chronic pancreatitis there were 8 cases of long-standing diabetes preceded by pancreatitis. Three of the 8 cases of diabetes were associated with pancreatic lithiasis and 5 were recurrent pancreatitis without lithiasis. There were 8 cases of pancreatic lithiasis but only 3 patients developed diabetes.

From a survey of the literature and my own observations it appears that permanent diabetes rarely follows acute pancreatitis, but that it frequently follows chronic pancreatitis. In the absence of calcification, diabetes develops in about 14 per cent, but about 45 per cent of subjects with pancreatic calcification develop diabetes.

Pancreatitis in Diabetics.—Acute pancreatitis may develop in a subject known to have had diabetes for a long time. Bossak[4] reported 8 of 106 and Richman[50] 8 of 58 cases of acute pancreatitis that developed in known diabetic persons. Guibal's[22] patient had diabetes for one year before an attack of pancreatitis. Comfort[11] reported that diabetes preceded the pancreatitis in one

of 7 cases in which the 2 diseases were associated. Schumacker[55] collected from the literature 19 cases in which diabetes preceded pancreatitis. Two of my 102 cases of acute pancreatitis developed in subjects with long-standing diabetes. The effect of acute pancreatitis in a diabetic subject is an intensification of the diabetic state.

However, only a small proportion of permanent diabetes is caused by pancreatitis. Sprague[60] observed 24 such cases which comprised 0.3 per cent of the diabetic population seen at the Mayo Clinic during a corresponding period. Among 2,089 cases of diabetes which I have studied at autopsy, only 8 were caused by chronic pancreatitis—an incidence of 0.38 per cent. The diabetes resulting from chronic pancreatitis differs from ordinary diabetes in the absence of vascular disease which is so characteristic of idiopathic diabetes. Sprague noted retinopathy in one of 24 subjects, but other observers do not mention vascular disease.

SUMMARY

One hundred and seventy-nine cases of fatal pancreatitis are reported. The incidence in necropsies in subjects over 20 years of age is 0.25 per cent in men and 0.36 per cent in women. The ratio of women to men with pancreatitis is about 3 to 2. In men 74 per cent and in women 84 per cent develop after the age of 40 years. The gross changes in the pancreas noted at necropsy were similar in the acute and chronic cases except that 20 per cent of the latter showed fibrosis, calcification, or pseudocysts.

The role of cholelithiasis in pancreatitis cannot be appreciated unless the cases are arranged with respect to age and sex. The excess of cholelithiasis in persons with pancreatitis above its expected incidence suggests that gallstones are the cause of pancreatitis in about one-third of men and one-half of women over 40 years of age. Gallstones are not an important factor in the etiology of pancreatitis in persons under 40 years of age.

Alcoholism is more important than cholelithiasis in the etiology of pancreatitis in subjects under 40 years of age. Thirteen of our 32 subjects with pancreatitis in this age group were chronic alcoholics, while only 6 had gallstones. In the literature 20 to 30 per cent of pancreatitis is attributed to alcoholism.

Lithiasis is usually a late complication of chronic pancreatitis but it may develop without signs of pancreatitis.

Glycosuria is not often found in mild cases of pancreatitis but is usually present in the later stages of severe cases. Hyperglycemia of some degree is usually present in all cases of severe pancreatitis.

Typical diabetes of short duration often develops in subjects who die several weeks after the onset of an acute attack. Permanent diabetes finally develops in about 14 per cent of subjects with chronic pancreatitis without lithiasis and in about 45 per cent of those with lithiasis. A diabetic may develop acute pancreatitis. Only a very small percentage of clinical diabetes is due to pancreatitis, 0.38 per cent in our necropsies. Diabetes due to pancreatitis differs from idiopathic diabetes in the absence of vascular disease.

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THE MECHANISM OF THE PATHOGENESIS OF PANCREATIC NECROSIS AND THE THERAPEUTIC EFFECT OF PROPYLTHIOURACIL

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INTRODUCTION

THE mechanism of the pathogenesis of pancreatic necrosis and the therapeutic effect of propylthiouracil are intimately related. The outstanding characteristic of the lesion in experimental pancreatitis as well as in the clinical disease is the rapid extensive and hemorrhagic necrosis which in many instances leaves the pancreas as a dark structureless gelatinous mass.

The mechanism of this necrosis is widely held to be due, one way or another, to the action of the proteolytic enzymes trypsin and chymotrypsin. Trypsin particularly is said to be the chief culprit. This is somewhat surprising in view of the well-known fact that no mammalian enzyme can seriously disturb, much less digest, a healthy well-nourished cell. Indeed, the cell membrane which first must be broached is not protein in nature and therefore not likely to be altered by a proteolytic enzyme.

Surgeons have long been aware that long-standing pure pancreatic fistulas do not cause necrosis. The mechanism of necrosis in experimental pancreatitis or indeed in the clinical disease assumes, therefore, an extraordinary importance for the surgeon as well as the experimentalist.

Ever since Starr stated at the Meeting of the Pan-Pacific Surgical Association in 1954 that propylthiouracil was beneficial in acute hemorrhagic pancreatitis, its mechanism of action in this disease has received our undivided attention.

It has been shown previously in this laboratory that propylthiouracil was not a specifically selective antithyroid agent, but that propylthiouracil inhibited the oxygen uptake in all organs and tissues.[20, 21] Less energy was released, less work was done, less products were formed, and so there would result a remarkable reduction in the tempo of metabolism with a clinical picture not unlike that of hypothyroidism.

This point of view has recently been supported by some powerful evidence. Propylthiouracil inhibits the growth of tobacco mosaic virus in a concentration of 4/100,000 molar.[4] In partially pancreatectomized rats, it delays the development and onset of diabetes. It causes adrenal atrophy and inhibition of growth[27] and bizarre cerebral manifestations.[26] Most important the synthesis of amylase in cell suspensions is inhibited by propylthiouracil.[9]

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In order to explain the mechanism of action of propylthiouracil in experimental pancreatitis as well as the mechanism of necrosis, the following working hypotheses were evolved, all of which were susceptible of being tested experimentally.

WORKING HYPOTHESES

1. The initial steps in pancreatic necrosis are a vascular lesion, loss of cell membrane continuity, disorganization of cell architecture, and extrusion of the intracellular enzymes which now act upon the cell contents as well as any surrounding inadequately irrigated cells to produce finally the picture of total necrosis.

2. Trypsin and chymotrypsin extracellular enzymes play no significant role in this process and the other enzymes in pancreatic juice have minimal effects and then only on already disorganized cells.

3. Propylthiouracil should delay the progress and minimize the extent of the lesion in experimental pancreatitis through its reducing the tempo of metabolism and placing the organ at rest when under stress. Less intracellular enzymes will be released and these are par excellence the agents of necrosis when in the presence of inadequately nourished cells or tissues.

METHODS

1. Measure the disorganization of energy mechanisms in liver, kidney, and heart as shown by inhibition of oxygen uptake, by pancreatic homogenates, pancreatic mitochondria, and the microsome fraction from the pancreas.

2. Compare the effect of crystalline trypsin, chymotrypsin, singly and in combination, trypsin inhibitor, and various types of pancreatic juice upon similar preparations.

3. Set up experimental pancreatitis by a method recently described by Pfeffer and associates[19] in a group of 12 dogs, one being sacrificed every hour for 11 hours and a second group of 12 dogs sacrificed at 21 hours as controls to compare with 13 dogs similarly prepared but receiving propylthiouracil and sacrificed at 21 hours.

RESULTS

1. The results of the action of pancreatic homogenates on heart, kidney, and liver are shown in Fig. 1 in which there has been an enormous inhibition of oxygen uptake by the degradative enzymes in the pancreas which have disorganized the oxidative energy organization in liver, kidney, and heart. The destructive capacities of a pancreatic homogenate on kidney homogenate for example is shown when, after adding 0.3 ml., no significant increased inhibition of oxygen uptake occurs even on adding up to one full milliliter. The pancreatic mitochondria are much less inhibitory as shown in Fig. 2. Other experiments show very convincingly that these destructive enzymes are predominantly localized in the microsome fraction. The 50 per cent ammonium sulfate precipitate of the microsome fraction appears to be the richest source so far discovered of these disorganizing enzymes.

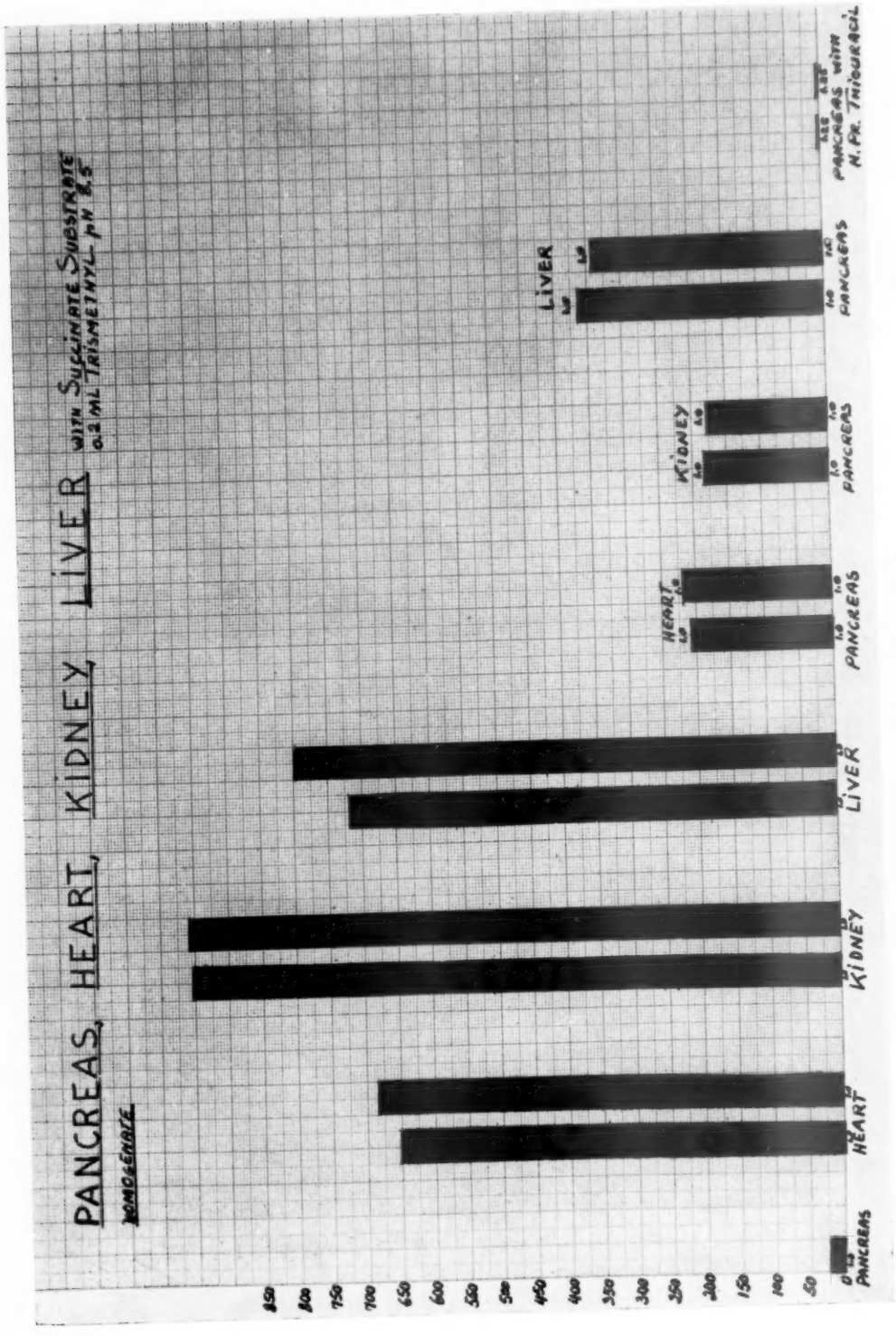

Fig. 1.—July 7, 1956.

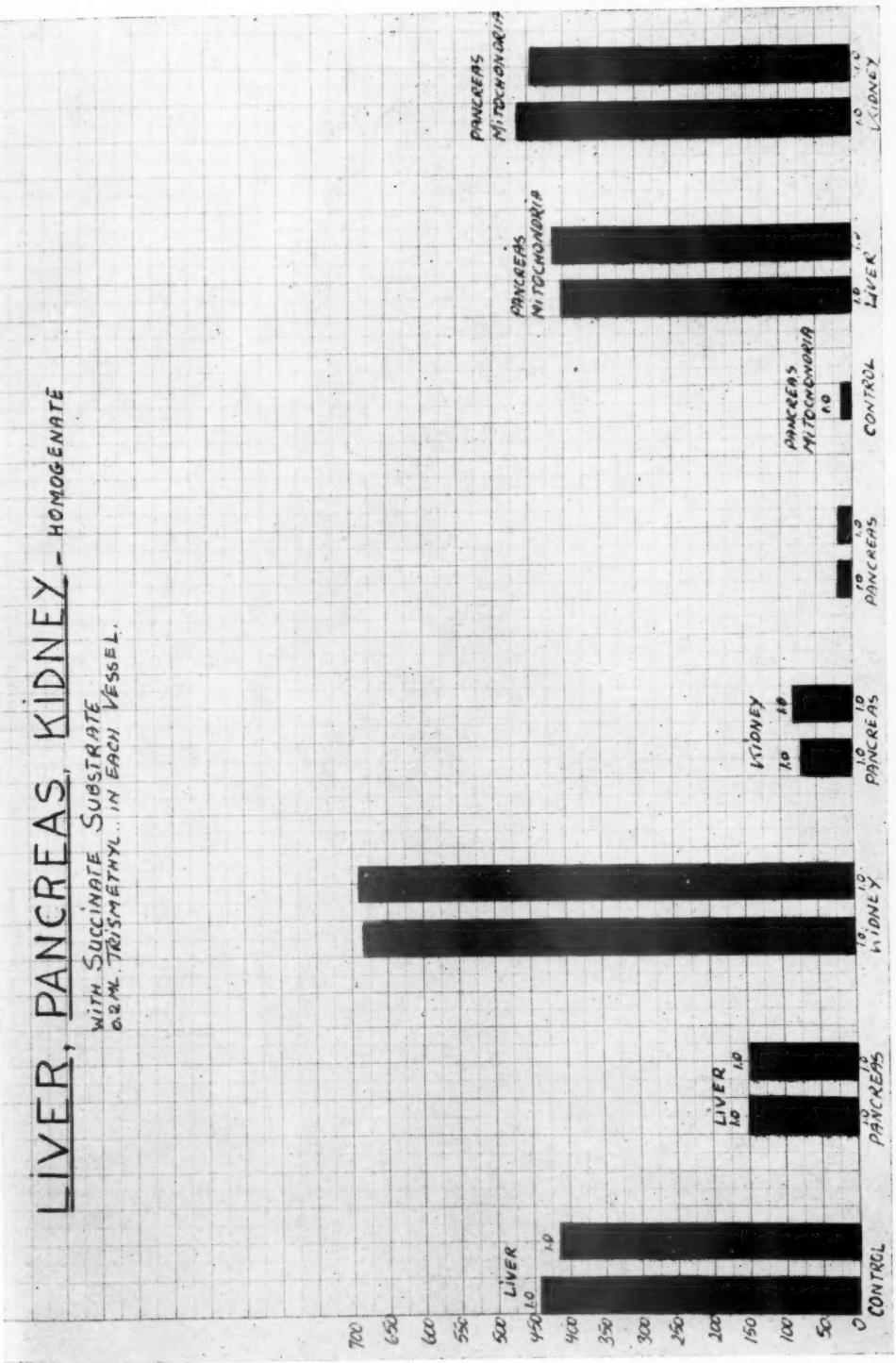

Fig. 2.—April 23, 1957.

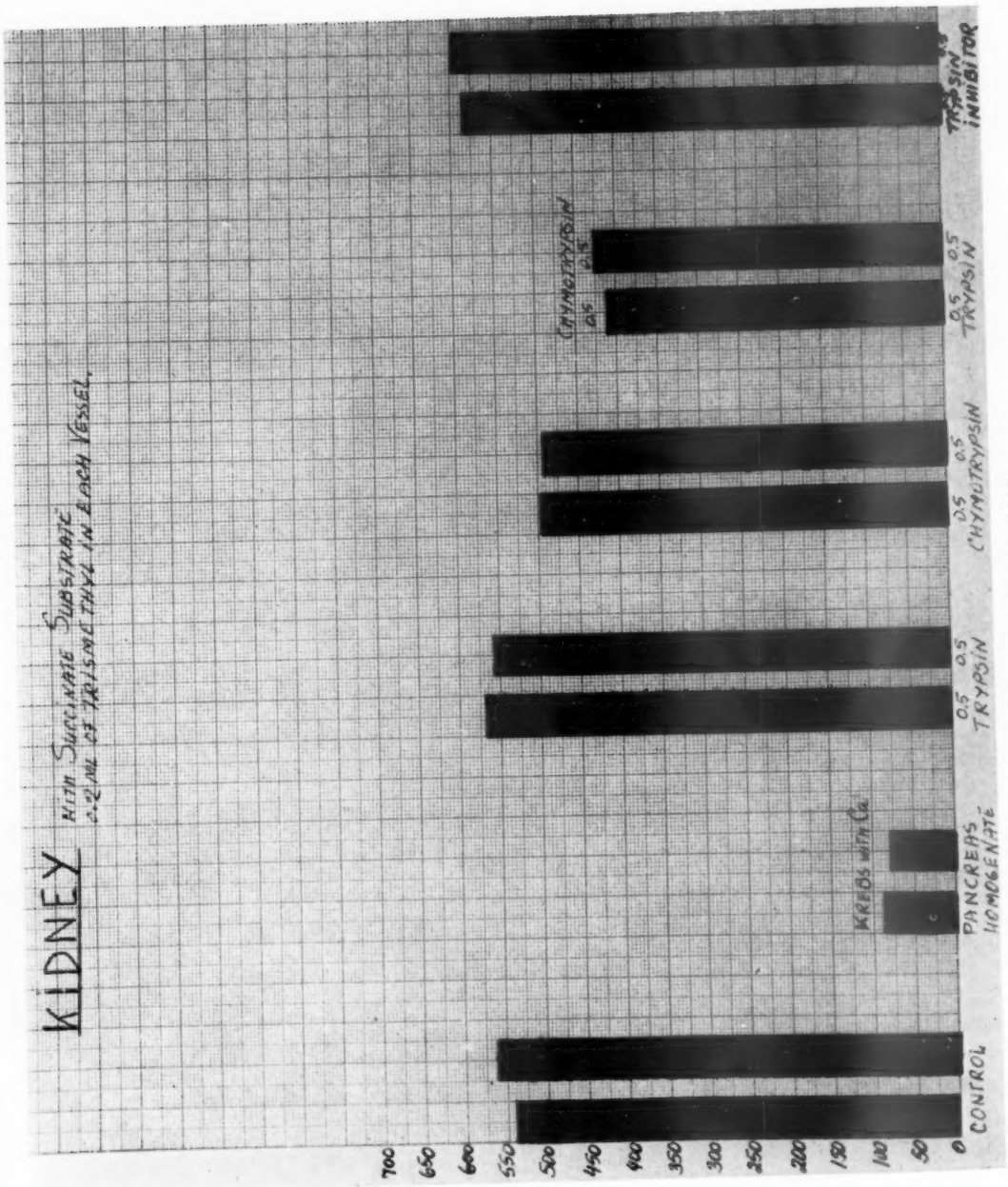

Fig. 3.—April 25, 1957.

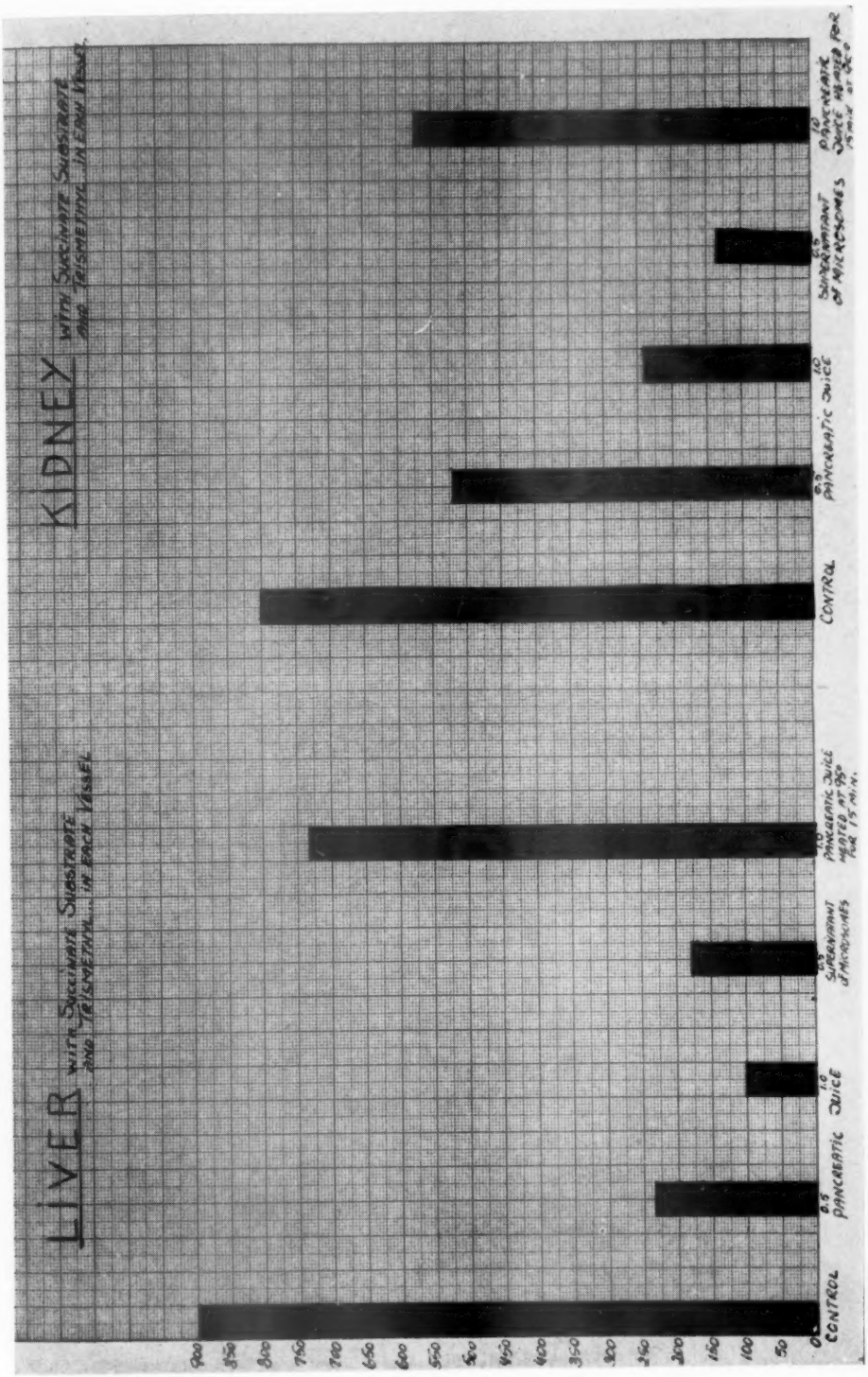

Fig. 4.—June 3, 1957.

Fig. 5.

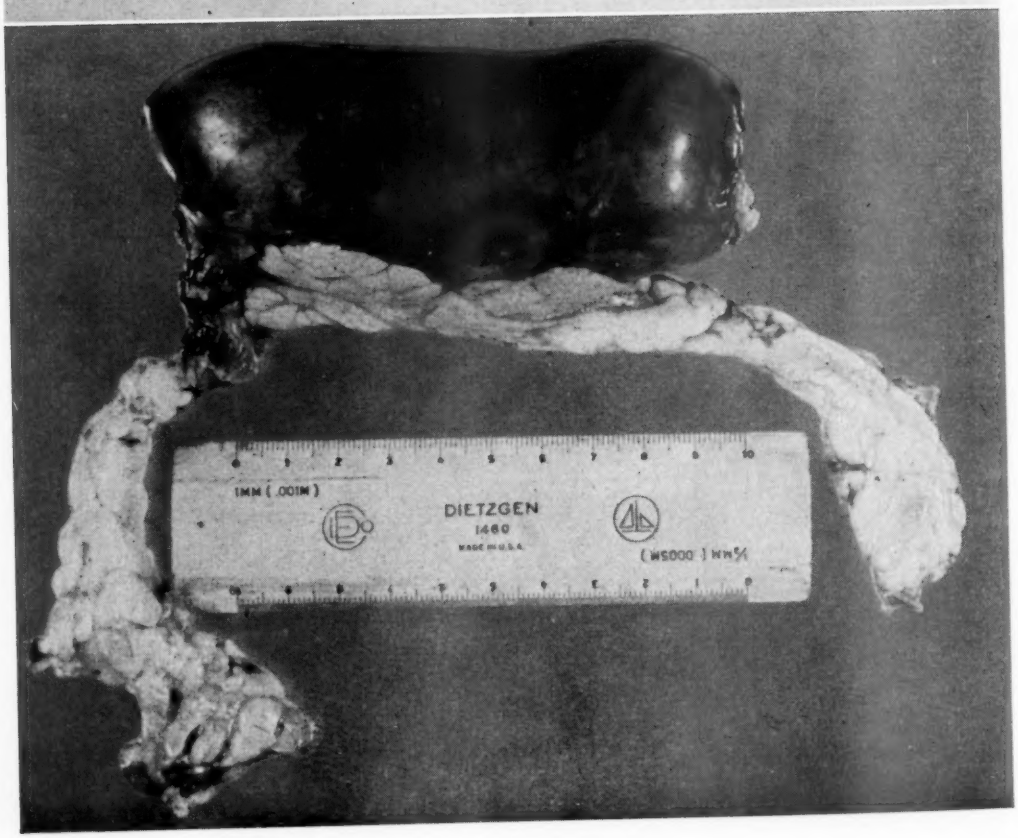

Fig. 6.

2. Fig. 3 illustrates the absence of any action of crystalline trypsin and crystalline chymotrypsin and trypsin and chymotrypsin together as well as crystalline trypsin inhibitor on the oxygen uptake of kidney homogenates.

The action of various types of pancreatic juice on homogenates of liver and kidney were tested. "Secretin" juice had no effect, "vagal" and "secretin" juice minimal effects. Fig. 4 shows the effect of pure "vagal" juice with marked inhibition of oxygen uptake. The heating of the vagal juice at 95° C. for 15 minutes removes a large percentage of its destructive capacity without interfering with the action of trypsin which is unaffected by such treatment. Even when one has mechanically ruptured the cells as in a true homogenate, pancreatic juice, the pure vagal juice is not as destructive as the pancreas homogenate and far less so than the microsome fraction. When liver homogenate is exposed to 0.5 ml. of pancreatic juice, the reduction in oxygen uptake is 70 per cent, the average of 2 vessels. When liver slices and liver mince are exposed to the same quantity of pancreatic juice, uptake of oxygen is inhibited on an average of 2 vessels 25 and 38 per cent, respectively, under the same conditions.

Upon the addition of liver homogenates to kidney or heart homogenates or various combinations of these tissues, there is no such effect noticeable as when one adds pancreatic homogenates.

Prophylthiouracil inhibits oxygen uptake in the homogenates of all organs and tissues and it is particularly active in inhibiting oxygen uptake in mitochondrial preparations. Less oxygen is used, less energy is released, less product is formed, and the organ is placed at rest.

In the photograph of a pancreas (Fig. 5) from the control group, the lesion has progressed to complete necrosis, while in the photograph of a pancreas (Fig. 6) from the experimental group, the progress of the lesion has been delayed and the degree of necrosis is minimal.

In the group given prophylthiouracil, 8 of 13 dogs had no gross evidence of pancreatitis except for some edema and congestion. Five animals showed a picture of acute hemorrhagic pancreatitis with areas of necrosis in the gland and scattered areas of fat necrosis. These changes were much less than those found in the controls with one exception.

The evidence from microscopic examination in general confirms the gross findings. A good summary of these findings would be that in the experimental group the findings at 21 hours were comparable to those present in the control group at 2, 5, or, at most, 11 hours.[18, 22]

DISCUSSION

One of the most impressive results of these experiments was the destructive effects of pancreatic homogenates upon the oxygen uptake of liver, kidney, and heart homogenates when measured by the usual manometric techniques. No other organ so far studied shows this disorganization activity by intracellular enzymes as does the pancreas. It is an arresting thought to realize that a quantity of less than 0.5 ml. of a pancreas extract when added to a homogenate of liver or kidney or heart reduces their oxygen uptake from the control of around 1,000 microliters per hour to less than 200 microliters. It is

most important to point out that these destructive disorganizing enzymes are normal intracellular physiologically active catalysts making possible the completion of a wide variety of chemical reactions and whose aggregate constitute cell metabolism. Indeed, these intracellular enzymes may very well be the builders of the enzymes which are extruded into the pancreatic juice.

In other words, the enzymes synthesizing the gland's products are responsible for the destruction of the oxidative energy release mechanisms in other organs and not the enzyme products formed by the pancreas and secreted into the pancreatic juice.

In a recent review, Dawson[5] has brought out that the structural integrity of the cell is dependent upon the presence of phospholipids; this is true of the cell membrane, mitochondria, microsomes, and even the nucleus. The phospholipids are continually being broken down and built up. These processes are in a dynamic equilibrium with a constant concentration being maintained.

Edwards and Ball[6] have suggested that phospholipids act as a cement substance for succinic oxidase and cytochrome oxidase, both systems containing high phospholipid content. This would make them exceedingly vulnerable to destruction from the action of phospholipases in the absence or restriction of outside supplies to crucially important links in the oxidative energy chain.

It is well known that after death the pancreas undergoes very rapid autolysis and, with the possible exception of the mucosa of the gastrointestinal tract and the adrenal cortex, is the most rapidly autolysed tissue in the body. These autolytic enzymes do not suddenly appear after death or indeed become activated but are always carrying out their catabolic activities. This does not become recognizable because simultaneously the synthetic enzymes are building up the cells as fast as they are being broken down. This dynamic equilibrium between these 2 forces of building up the cell and breaking it down are usually described as the dynamic state of body constituents.[23] The tempo of these changes is a controversial subject at the moment; nevertheless it seems reasonably certain that there is a very rapid turnover of the metabolic proteins in protein synthesizing glands and a slower turnover of the structural constituents.[15] It may well be oversimplified, but it is clarifying to state that the catabolic enzymes have all their requirements available within the cell and therefore continue their activities even after death. The anabolic enzymes on the other hand, require supplies from outside the cell and when these are cut off all synthetic activity ceases and the effects of those enzymes breaking down the cell rapidly becomes obvious in histologic and anatomic changes.

It is somewhat surprising at first sight that the pancreas, an organ weighing about 150 grams, synthesizes more protein than any other organ including the liver and reticuloendothelial system with the single exception of the gut and per gram of tissue has by far the greatest protein synthesizing capacity of any structure in the body.[3, 8, 25] This means that there must be a high concentration of protein synthesizing enzymes and, if, as has been suggested by Bergman,[2] proteolytic activity is merely a reversal of the direction of equilibrium from that of protein synthesis, then proteolysis would be the reverse of protein synthesis with the same enzymes operating and should be most rapid after death where protein synthesis has been most active during life. This has

been shown to be true in the pancreas, and upon this basis the destructive capacity of the intracellular enzymes from the pancreas upon the oxidative energy release mechanism in other parenchymatous organs probably should not be too surprising.

When one compares the action of pancreatic extracts on other organs and homogenates with the absence of any effect of enormous concentrations of crystalline trypsin, crystalline chymotrypsin, and trypsin and chymotrypsin together as well as crystalline trypsin inhibitor, surely trypsin cannot possibly explain any clinically observed necrotic process. Indeed, trypsin has such a specific site of action on the amino acid sequence in a protein[16] that its disorganizing effects by itself are quite limited. It only attacks specific linkages, and if none of these are on the surface of the protein no action will take place.

When one adds a concentrated pancreatic vagal secretion to similar systems as other organ homogenates, there is a definite interference with the oxidative energy release mechanism as shown by the inhibition of oxygen uptake, but here other enzymes such as pankrin,[10] carboxypeptidases, lipases, phospholipases, elastase, leicithinases, esterases, and so forth have an effect on already mechanically ruptured cells. But in the case of organized tissue, such as slices or mince, the effect is very much less. When an active disorganizing pancreatic juice is heated to 95° C. for 15 minutes, trypsin is not effected; but one can see there is an enormous decrease in the destructive capacity of the pancreatic juice. "Secretin" juice from the pancreas has no significant effect on any of these preparations.

Protein synthesis is almost completely abolished by the pancreas during anoxia[12] and one may therefore assume that the synthetic processes are dependent upon an oxidative energy release mechanism. This is markedly inhibited by propylthiouracil which does not appear to interfere with glycolysis.

If one reduces the expenditure of energy for synthetic processes with propylthiouracil, this must place the gland at rest and the energy requirements to maintain the anatomic integrity of the cell would be much reduced which here is of such crucial importance in preventing the escape of the intracellular enzymes with their enormous potentiality for destruction. So important is this in the pancreas that, even in widespread necrosis from feeding ethionine, the protein production of the gland actually increases[24] and, upon stopping the ethionine, the re-establishment of normal cell structure is incredibly rapid.[7] In addition, after an insult of heavy radiation the pancreas goes right on building and excreting new protein at an increased rate.[13]

As long ago as 1904, Barcroft and Starling[1] stated that there is an increased oxygen consumption during pancreatic secretion regardless of the blood flow. Also oxidation was at a higher tempo in the pancreas than in the body generally. The pancreas has an almost inexhaustible capacity to build new protein and even after 14 hours of continuous stimulation its productive capacity remains undiminished.[11]

It seems like ordinary prudence, when for any reason supplies going to the pancreas are restricted, to reduce the energy expenditure utilized in the synthesis of new enzymes for excretion and to conserve all possible cell resources to facilitate the maintenance of organ structure. This takes on increased significance,

for example, when it is realized that, in B subtilis, alpha amylase formation and cell growth are inversely related.[17] Therefore it would seem that while enzymes are being secreted there is a loss of efficiency in building structural components.

In the experimental group of animals receiving propylthiouracil, the delay in the progression of and definite limitation of the necrotic process as compared to the controls would seem to be the result of the reduction in the synthetic work expenditure; for example, production of extracellular enzymes. More materials would now be available to maintain cell structure and more energy at hand to constructively use these materials.

In the pancreas from the experimental animal the whole process has been modified by propylthiouracil as compared to the control.

It has recently been shown by Jeener[14] that thiouracil becomes incorporated into the pyrimidines and this renders the ribonucleic acids unable to contribute to protein synthesis. This effect if operative here, would be additional to the inhibition of the oxidative energy release mechanism in reducing production and would still further contribute to placing the gland at rest when under stress.

An extraordinary, pertinent remark has recently been made by H. A. Krebs: "Cells are leaky ships and only kept afloat by the pumps." For our purposes the cells of the pancreas are the most leaky of any in the body and, once there is an interference with delivery of supplies for the pumps, the pumps fail and the cells rapidly become submerged.

SUMMARY

1. Evidence has been presented to suggest that the mechanism of the necrosis in experimental or even clinical pancreatitis is essentially the result of a vascular lesion, loss of cell membrane continuity, and escape of intracellular degradative enzymes which destroy all inadequately irrigated pancreatic or other organ cells with which they come in contact.

2. It has been shown that trypsin and chymotrypsin play no significant role in this process.

3. The disorganizing activities of pancreatic juice are due to enzymes other than trypsin and chymotrypsin. The action of any type of pancreatic juice is of small practical significance in either the experimental or clinical disease. Indeed, the more severe the disease the less the pancreatic secretion will play a role.

4. Propylthiouracil inhibits oxidative energy release, less work is performed, less product is produced, less supplies are consumed, and as a result the gland is placed at rest when under stress.

5. In view of the enormous destructive capacities of the intracellular pancreatic enzymes, the maintenance of the morphologic integrity of the cells becomes of the utmost importance. By cutting down the synthesizing activities of the gland, it should allow more materials and energy to be available to maintain cell structure in the presence of restricted supplies because of some

vascular derangement. Accordingly, propylthiouracil should be clinically beneficial, as it has been shown to be, in the delay and limitation of the necrotic process in the experimental lesion as compared to the controls.

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ACUTE HEMORRHAGIC PANCREATITIS

A Safe, Effective Technique for Diagnostic Paracentesis

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INTRODUCTION

PROVIDED the correct diagnosis can be made, most surgeons[2, 7, 16] agree that laparotomy should be avoided in acute pancreatitis. Unfortunately, the standard resources of history, physical examination, x-ray studies, and laboratory findings more often than not fail to establish the diagnosis. The hope that serum amylase would be specific for pancreatitis must be abandoned, as Elman[3] has recently pointed out. Elevated serum amylase values have been reported in perforated duodenal ulcers,[10] acute cholecystitis,[18] renal insuffciency,[8] cerebral trauma,[13] and ectopic pregnancy.[6] Even the administration of opiates can sometimes bring about significantly increased amylase levels.[4, 11]

In order to spare the patient surgery with high risk and little or no benefit, we have, in the past year, employed the modified paracentesis procedure to be described. Several authors[9, 15, 17] have recently shown renewed interest in the diagnostic importance of this procedure. As Keith, Zollinger, and McCleery[5] first pointed out, hemorrhagic (prune juice) peritoneal fluid containing high amylase values is pathognomonic of acute hemorrhagic pancreatitis. Dissatisfied with the risk of using sharp, beveled needles and with frequent failure to recover fluid by standard aspiration methods, we have employed the procedure described below.

METHOD

The skin is prepared with aqueous Zephiran and 3 to 4 c.c. of 1 per cent procaine is injected. The site of the tap is usually the right lower quadrant about 3 cm. below the umbilicus just at the lateral rectus border. If no fluid is obtained a similar location on the left side is used. With a No. 11 stab blade a 3 mm. incision is made in the skin to allow the comfortable introduction of a No. 13 B-D thoracentesis needle and trocar. The needle is gently inserted and one can feel the "pop" as it passes into the peritoneal cavity. At this point the patient generally experiences parietal peritoneal pain as an added assurance that the needle has passed into the peritoneal cavity. The trocar is then removed and aspiration is attempted with a 20 c.c. syringe. If fluid is not obtained a No. 60 size polyethylene catheter approximately 18 inches long is threaded through the needle upward toward the foramen of Winslow (Figs.

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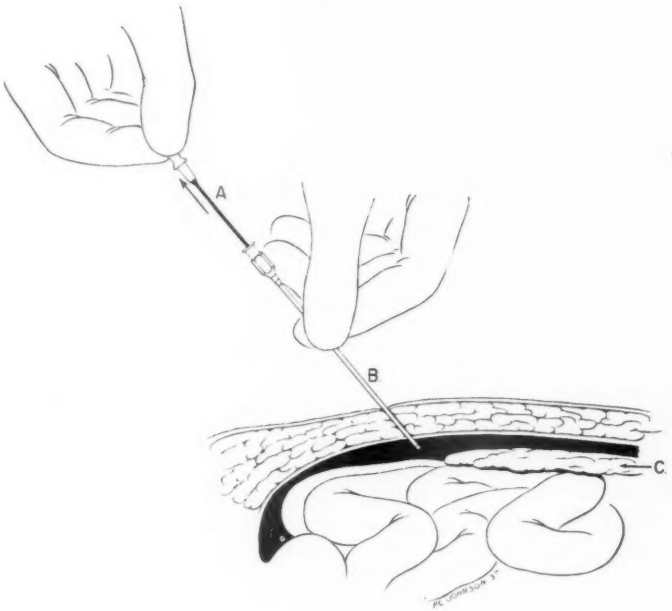
1 and 2). The needle is then removed while the polyethylene catheter remains in place. This maneuver allows the patient to be turned into several positions in an effort to obtain fluid. Our positions for attempted aspiration consist of the following sequence: (1) flat in bed, (2) right lateral decubitus, (3) left

Fig. 1.



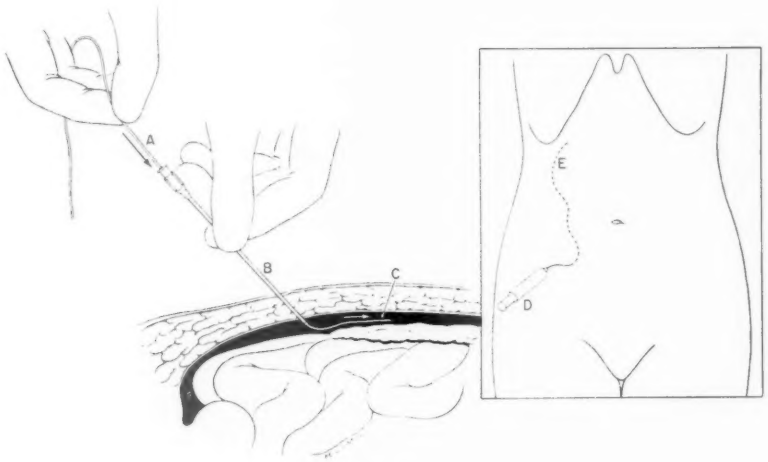


Fig. 2.

Fig. 1.—Needle (*B*) in place in peritoneal cavity. Trocar (*A*) being withdrawn. Omentum (*C*).

Fig. 2.—Polyethylene catheter (*A*) inserted through needle (*B*) being directed toward foramen of Winslow (*E*) anterior to omentum (*C*). Inset shows aspiration by syringe (*D*).

lateral decubitus, (4) bed inclined upward to 45 degrees, (5) start removal of catheter, and (6) repeat on left side if no fluid is obtained.

The use of the flexible polyethylene catheter averts any possible danger of bowel injury and allows the patient to be moved into several positions, thereby

increasing the chance of obtaining fluid. We have used this procedure on 27 different occasions without incident and have obtained fluid for analysis 10 times. Ten patients in the series underwent exploratory laparotomy and the presence of fluid was confirmed. In the one instance of a "dry" tap, hemorrhagic fluid was found to be trapped in the lesser sac and not present in the general peritoneal cavity. Contraindications to the procedure are a scar at the puncture site, abdominal distention of moderate to marked degree, and the palpation of a mass in the region of the proposed tap.

One precaution must be observed. If an x-ray for free air is desired it should always be done before aspiration, since air may be introduced during the procedure. The amylase activity is determined by the method of Norby as modified by Agren and Lagerlof.[1]

DISCUSSION

In order to assure ourselves that a hemorrhagic peritoneal fluid with a high amylase was specific for acute hemorrhagic pancreatitis, we set out to analyze fluid obtained in various acute and chronic disease states. The results of 33 separate determinations are listed in Table I. It can readily be seen that the highest values for amylase are consistently seen in acute hemorrhagic pancreatitis as compared to the other conditions. The amylase values for ulcers which perforate into the general peritoneal cavity are elevated in many instances. However, in no case was as high a level reached as those present in hemorrhagic pancreatitis. Furthermore, the character of the fluid obtained in perforated ulcers was markedly different. In most cases there was a typical amorphous, fibrinous sediment which readily appeared with centrifugation or short periods of standing. Most often the fluid was yellowish to gray in color. In only one instance was it blood-tinged and this resembled the coffee-ground material obtained in the Wangensteen suction drainage. Three cases of perforated ulcer were alkaline to nitrazine paper, 2 neutral, and 5 acid; this test was of limited value in distinguishing the origin of the fluid.

TABLE I

SOURCE OF FLUID	AMYLASE (MG. %)
Thoracentesis fluid (5)	
4 Carcinoma with pleural effusion	0
1 Postoperative pleural effusion	0
Peritoneal fluid (28)	
5 Carcinomatosis	0-390
1 Ruptured spleen	240
4 Cirrhosis of liver	0
1 Perforated biliary cyst of liver	200
10 Perforated gastroduodenal ulcers	190-4,820
1 Intestinal obstruction without gangrene	10
1 Intestinal obstruction with 3 feet of gangrenous bowel	130
1 Acute edematous pancreatitis	1,700
4 Acute hemorrhagic pancreatitis	7,800-19,600

Two of our cases were very dramatic in confirming the diagnosis.

CASE 1.—This was a 63-year-old Negro man with history of epigastric pain, nausea, and vomiting of 12 hours' duration. Physical examination revealed a generalized peritonitis.

Serum amylase drawn on admission was 3,480 mg. per cent (normal 0 to 450 mg. per cent). A peritoneal tap yielded 1 c.c. of hemorrhagic fluid with an amylase level of 7,800 mg. per cent. On the basis of this test the patient was treated conservatively and made a rapid recovery.

CASE 2.—This was a 76-year-old white man with a vague history of abdominal pain and vomiting. Physical examination revealed left upper rectus muscle spasm and x-rays were negative for free air. An abdominal tap yielded 15 c.c. of turbid grayish blood-tinged fluid with an amorphous sediment and an amylase of 400 mg. per cent. On the basis of this a laparotomy was performed and a perforated ulcer on the anterior duodenum was closed.

It would seem that peritoneal aspiration should be used more often. In the face of peritonitis, the serum amylase has a definite value as a guide to diagnosis, but in and of itself has many serious limitations. At least 2 deaths have been recorded recently[12, 14] when absolute reliance was placed on the serum amylase level. On the other hand, great significance for diagnosis can be given to a hemorrhagic peritoneal fluid with a high amylase value. By obtaining such fluid through peritoneal aspiration one should be strongly influenced to treat the patient conservatively.

SUMMARY

A technique for obtaining peritoneal fluid by use of a polyethylene catheter has been outlined. This procedure has yielded peritoneal fluid in all known instances when it was present. Hemorrhagic peritoneal fluid with a high amylase value is pathognomonic of acute hemorrhagic pancreatitis, whereas elevated serum amylase values are not. Aside from exploratory laparotomy this seems the only way to assure the diagnosis and thus allow conservative treatment of the patient.

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RISE IN SERUM BILIRUBIN WITH BILIARY OBSTRUCTION AND ITS DECLINE CURVE AFTER OPERATIVE RELIEF

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IN THIS paper we wish to present data which are used to describe the curve of decline of the serum bilirubin level after the operative relief of obstructive jaundice in man. A formula for this decline curve of the serum bilirubin would enable the surgeon to predict roughly when its level should revert to normal in individual patients undergoing operation for the relief of obstructive jaundice. If there were gross departure from the predicted course, the possibility would arise that the operation had been inadequate.

There are, of course, no satisfactory data concerning the rate of rise of the serum bilirubin with the onset of complete biliary obstruction in man. Inevitably when the duct has been accidentally ligated or obstructed at operation, little useful information is forthcoming. In a single patient we have had an exceptional opportunity to observe the rise of the serum bilirubin following the development of complete biliary obstruction and to estimate its level regularly, thereafter, for some 12 months. This patient's data are used to sketch a theoretic curve of increase of the serum bilirubin with complete-on-partial obstruction.† It is helpful to examine the factors involved in the rise of the serum bilirubin before describing its characteristic curve of decline after the relief of obstruction.

MATERIAL AND METHODS

Decline Curve of Serum Bilirubin.—One hundred and eighteen estimations of the serum bilirubin were made in a series of 17 patients operated upon for obstruction of the common bile duct, due to gallstones in 14 and cancer of the ampulla of Vater or the head of the pancreas in 3. In each case a large tube was inserted into the common duct at operation so that there was free drainage of bile throughout the observations. The serum bilirubin content was estimated by the method of Powell[5] before and at regular intervals after operation for periods of up to 11 weeks.

Concentration of Bilirubin in the Bile.—The bile draining from the tube in the common duct was collected and measured and its bilirubin concentration was estimated daily by Powell's modification of the diazo reaction. The bile was diluted 5 to 40 times with water to give a bilirubin concentration between

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†The expression "complete-on-partial obstruction" is used to signify progressive obstruction which finally becomes complete.

1.2 and 6 mg. per milliliter. This gives a suitable concentration of diazotized bilirubin for reading in the Hilger biochemical absorptiometer using a green filter. Calibration of the absorptiometer was done with a standard solution of bilirubin in chloroform prepared from crystalline bilirubin and checked by measuring the absorption co-efficient at 450 mμ in a Hilger Uvispek spectrophotometer. These methods give an accuracy of ± 5 per cent, provided care is taken with the preliminary dilution of the bile, which, due to its viscous nature, is difficult to pipette accurately.

In 24-hour specimens of bile, the bilirubin is readily oxidized to biliverdin; also bacterial activity converts bilirubin into urobilin. The tubing and collecting apparatus must be thoroughly cleansed before use. The collecting bottle at the bedside is emptied at 6-hour intervals into the 24-hour flask which is kept refrigerated in the dark. Aureomycin HCl in concentrations up to 100 mg. per cent does not interfere with methods for estimating bile pigments and, added to the collecting bottle every 6 hours, is useful for preventing bacterial growth. From estimations of the relative proportions of bilirubin, biliverdin, and urobilin in 24-hour specimens of bile, it was determined that, provided no gross infection is present and the conditions of collection are satisfactory, bilirubin by the diazo method amounts to 80 to 100 per cent of the total pigment (Middleton, Cass, and Rundle—unpublished data). It may thus be used to follow the general trend of bile pigment excretion.

CASE REPORT

Complete Biliary Obstruction in Man (Case 1).—A physician, aged 48, a keen and accurate observer, was an associate in our laboratory. Early in May, 1955, he first noticed anorexia and epigastric discomfort chiefly before meals. He asked to be examined by one of us (F. F. R.) on June 20, stating that he had gradually lost 7 pounds in weight during the past 6 weeks. The only definite finding was slight tenderness in the right hypochondrium. No icterus of the skin was noted.

However, on the following day he felt itching of the skin and 2 days later he noticed that the skin and conjunctivae were slightly jaundiced, that the stools were pale, and that the urine was dark. The cause of the obstruction was subsequently demonstrated to be a carcinoma at the junction of the hepatic ducts, an adenocarcinoma with marked fibrous tissue reaction. At laparotomy on July 7, 2 weeks after the onset of jaundice, the gall bladder and common duct were strikingly collapsed and shrunken.

At a second operation on August 29, cholangiography showed that, at the level of the porta hepatis, the flow of opaque medium was completely blocked even when it was injected into the common duct under pressure. All efforts to cannulate the right hepatic duct were unsuccessful but, after some difficulty, a cannula was pushed up into the left duct. Further cholangiography then showed tremendous dilatation of the left hepatic duct above the block. We may conclude that he suffered from complete-on-partial biliary obstruction. It is likely that the obstruction finally became complete at about the time when he first presented for examination. At all events the existence of complete obstruction was proved 2 to 3 weeks afterward and this obstruction remained unrelieved for more than one year. Supervoltage therapy and the establishment of a small external biliary fistula may then have modified its extent.

RESULTS AND DISCUSSION

Rise of Serum Bilirubin in Obstructive Jaundice.—Curve *C* in Fig. 1 gives a complete record of the observed serum bilirubin levels in Case 1. Two other

curves, *A* and *B* (Fig. 1), are drawn for comparison. Curve *A* shows the theoretic linear rise to be expected in the serum bilirubin level, assuming that the common hepatic duct were suddenly completely blocked at zero time and that no other route of elimination of the bile pigments existed.

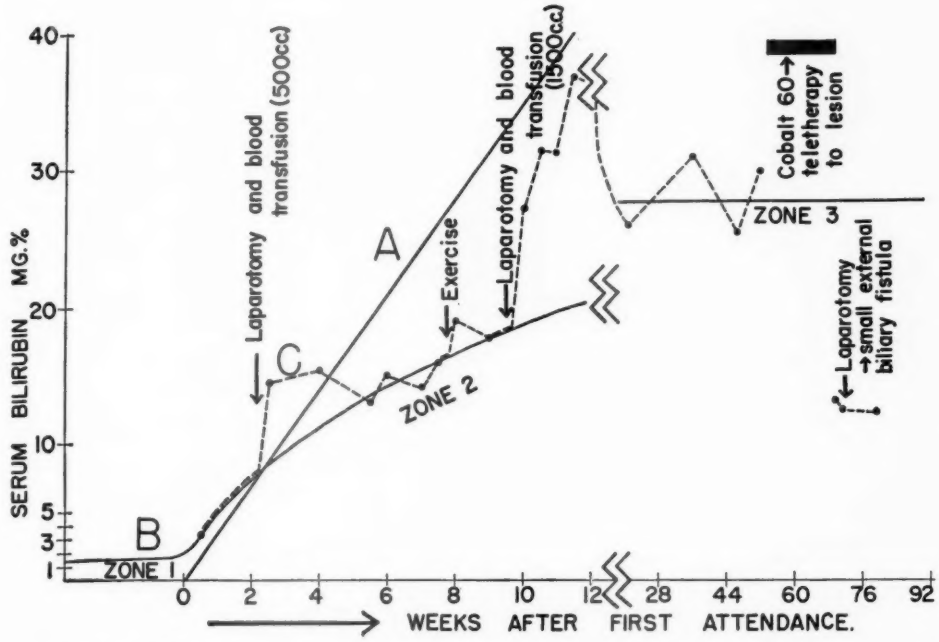

Fig. 1.—Rate of rise of serum bilirubin in complete biliary obstruction. Curve *A*, theoretic curve of serum bilirubin increase following sudden complete obstruction at zero time, assuming normal bile pigment production and no urinary or other leakage. Curve *B*, theoretic curve with gradually increasing obstruction, becoming complete at zero time, *zone 1* to left of zero time, *zone 2* from 0-20 weeks approximately, and *zone 3* from 20 to 60 weeks. Curve *C* shows the observed values of the serum bilirubin in Case 1 and a suggested curve showing step-wise rise with each of 2 operations. The duration of the first operation was 2 hours and 1 unit (500 c.c.) of blood was transfused; the second operation was more extensive and lasted 4½ hours and 3 units (1,500 c.c.) of blood were given.

Because the observations were so protracted the time scale is interrupted and changed at 12 weeks. From 51 to 67 weeks teletherapy with cobalt 60 was given to the region of the porta hepatis and just above. Seventy weeks after the observations began a final laparotomy was done and a small tube was inserted with difficulty into the left hepatic duct above the porta. But this tube only drained small quantities of bile (60 to 300 c.c. daily).

In curve *A* it has been assumed that, in obstructive jaundice, bilirubin production is maintained at its normal level of about 250 mg. daily. The rise in the serum bilirubin would then proceed at the rate of 0.5 mg. per day, assuming a total body water of 50 L. and that the added bilirubin were evenly distributed throughout it.* It is, of course possible, that in obstructive jaundice the retained bilirubin is unevenly distributed and that even its rate of production is affected, but these factors would change the slope rather than the shape of curve *A*.

Curve *B* is a suggested theoretic curve for the level of the serum bilirubin in complete-on-partial obstruction due to fibrosing carcinoma in the absence of operative or other treatment. This curve may be divided into 3 zones or stages

*The values for bilirubin production and total body water are not known precisely but those given are estimates for healthy adult males and suffice to illustrate the argument.

for descriptive purposes. During the first, the serum bilirubin level rises imperceptibly over a period of weeks or months. During this stage there is increasing anatomic obstruction but physiologic mechanisms, probably brought into action by minor rises in the serum bilirubin, compensate for it. These mechanisms include the secretion of bile containing a higher concentration of bilirubin and leakage of bilirubin in the urine. There is evidence (Fig. 2) that the power of the liver to concentrate bilirubin is very great and it is likely that until anatomic obstruction becomes virtually complete there is little physiologic obstruction, so that jaundice remains at subclinical levels.

There then follows *zone 2,* when blockage of the duct becomes complete. Compensation is no longer possible. The serum bilirubin level rises sharply. Recently Billing, Lathe, and Cole[1] have shown that, in its passage through the liver cells, bilirubin is conjugated with glucuronic acid, forming an ester diglucuronide in the bile. The direct-reacting bile pgiments present in the serum in obstructive jaundice are the mono- and diglucuronides of bilirubin. Unlike bilirubin, they are water soluble and can therefore be excreted in the urine. The concept of a renal threshold for direct bilirubin was earlier abandoned by With.[8]

It is likely that, as the level of the serum bilirubin rises, its excretion in the urine will increase about in proportion to the excess concentration. Because of the rise which has already occurred in *zone 1,* little further accumulation (at the rate of 0.5 mg. per day) of pigments in the body fluids would be necessary to produce jaundice, which is usually quite evident at a serum bilirubin level of 3 to 4 mg. per cent. Thus the symptoms pale stools, dark urine, and jaundice would appear almost simultaneously.

Throughout *zone 2* of curve *B,* the rate of rise of the serum bilirubin is being slowed down progressively because of the loss of increasing amounts of bile pigment in the urine. The kidneys are probably excreting a constant proportion of the excess bilirubin present in the body fluid and finally this proportion equals the daily production of bilirubin, so that a plateau, *zone 3,* is reached. The height of this plateau, located at about 30 mg. per cent in Case 1, presumably varies with the patient's powers of renal clearance of bilirubin.

Curve *C* is the observed curve of the serum bilirubin in Case 1. Its rise is even sharper than that of the hypothetical curve *A,* in which no leakage is assumed and all the bilirubin normally produced is retained in the body fluids. This abnormally rapid rise could only be explained by abnormal loading of the serum with bilirubin. It will be noted that curve *C,* in fact, rose in step-wise fashion with each of 2 operations, and, possibly also, with an episode of unwonted physical activity.

In 1847, Virchow[7] first indicated that bile pigments were formed by the breakdown of hemoglobin when he showed that "hematoidin" found in old hematomas was similar to bilirubin; and, in the classical experiments of McMaster and associates[3] on dogs with biliary fistula, it was observed that surgical

traumas and exercise increased the daily output of bilirubin. The shaded areas between curves *C* and *B* are thus a function of the excess bilirubin load induced by these factors in Case 1; such excess was eliminated gradually by the kidneys so that curves *C* and *B* then merge.

Biliary Concentration of Bilirubin.—As might be expected the liver is a much more efficient eliminator of bilirubin than the kidneys. In the absence of obstruction it quickly excretes the abnormal load resulting from major surgical traumas. And it does this successfully despite a greatly reduced volume flow of bile after surgery.[6, 9] Thus jaundice rarely becomes evident during the postoperative period. Fig. 2 shows the mean curve of the biliary bilirubin concentration in the series of 17 patients; in all but 3, the gall bladder had been removed. The peak concentration on the second postoperative day is produced by normal plus abnormal bilirubin loading in the presence of a greatly reduced volume flow of bile.

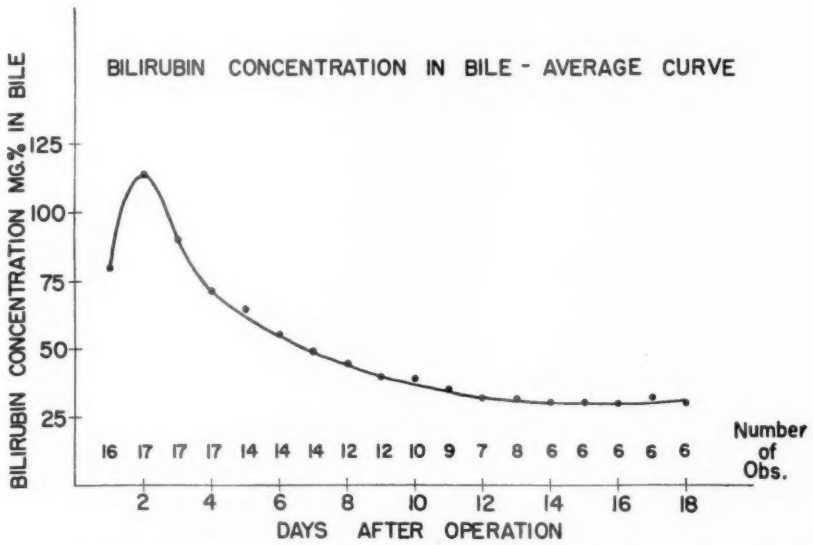
BILIRUBIN CONCENTRATION IN BILE - AVERAGE CURVE
BILIRUBIN CONCENTRATION MG.% IN BILE
125
100
75
50
25
16 17 17 17 14 14 14 12 12 10 9 7 8 6 6 6 6 6
Number of Obs.
2 4 6 8 10 12 14 16 18
DAYS AFTER OPERATION

Fig. 2.—Curve of mean bilirubin concentration in the bile draining after choledochostomy. In 14 of the patients, the gall bladder had been removed.

Decline of Serum Bilirubin After Relief of Obstruction.—Fig. 3 shows typical curves of the serum bilirubin after choledochostomy for obstructive jaundice. In Case 2 the obstructive lesion was a carcinoma in the head of the pancreas, and in Cases 3 and 4 gallstones were removed from the common bile duct.

In Cases 2 and 3, after an initial fall, there is a kick-up in the serum bilirubin level, and in Case 4 this is seen before any decline occurs. This "secondary" rise in the serum bilirubin level coincides in time with the maximal concentration of the biliary bilirubin (Fig. 2). However, it is an index of the efficiency of the liver as an excretory organ that this secondary rise in the serum bilirubin is so slight. The liver "clears" the postoperative load so quickly that there is little backing up of bilirubin in the body fluids.

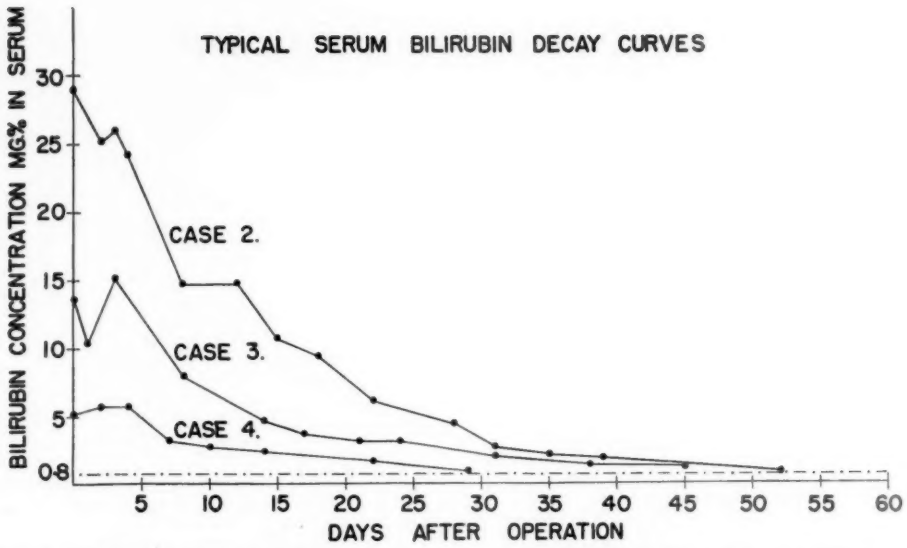

Fig. 3.—Typical decay curves of the serum after the relief of obstructive jaundice. Note secondary rise in level 2 to 3 days after surgery and increasingly gradual fall subsequently.

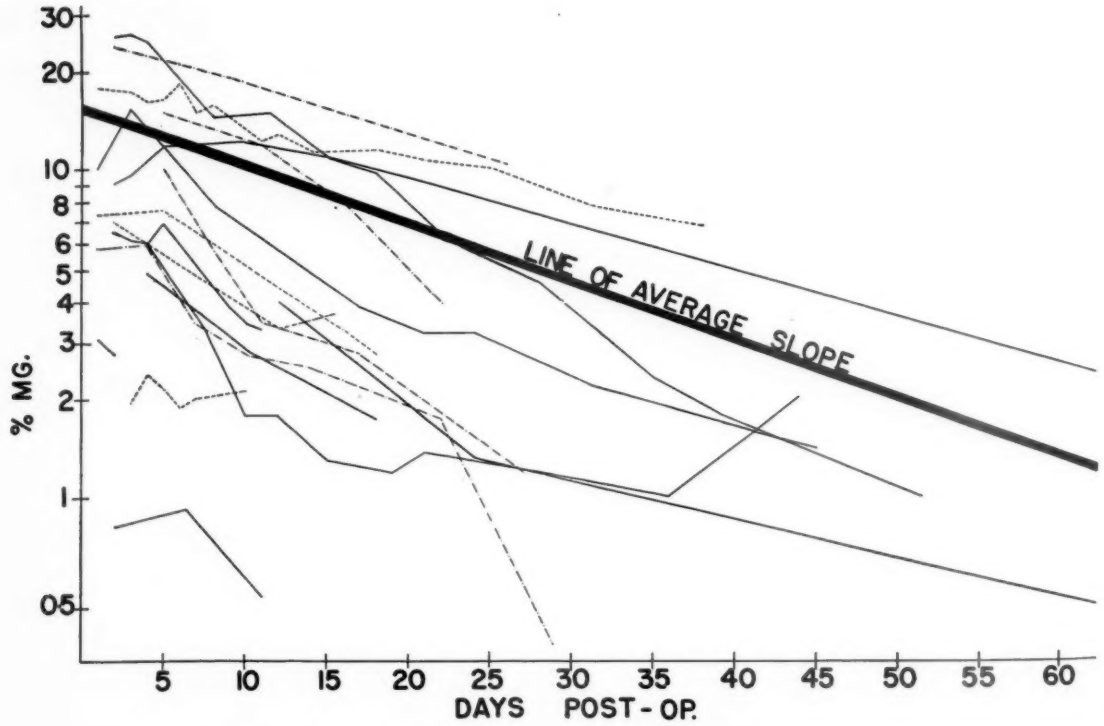

Fig. 4.—Exponential fall in level of serum bilirubin after relief of obstructive jaundice. Values from the postoperative peak onward are plotted logarithmically. Individual patients' curves (light lines) run approximately parallel to the curve of average slope, which reaches a half-value in 17.4 days.

Rate of Decline of Serum Bilirubin.—The shape of the curves in Fig. 3, after their secondary peak, suggests that they are exponential in character, with the serum bilirubin falling by a constant proportion each day.

In Fig. 4 the values of the serum bilirubin from the peak of the secondary rise onward are plotted logarithmically; individual patients' curves were shown as thin lines. The curve of average slope is drawn as a heavy straight line and it will be seen that the curves of individual patients run reasonably parallel to it.

The line of average slope is such that, after the relief of obstruction, the serum bilirubin falls by one-half in approximately 17.4 days. In other words, if x is the serum bilirubin concentration at t days after the postoperative peak, and x_o is the peak concentration, $\frac{x}{x_o} = e^{-0.04\,t}$ or $\log_{10}x = \log_{10}x_o - 0.0173\,t$. Thus in a patient with a serum bilirubin level of 12 mg. per cent 2 to 3 days after operation, it may be predicted that the jaundice will have disappeared in approximately 35 days, when the level will be about 3 mg. per cent. Individual patients will show variation from the average fall, but, clearly, if there is gross departure (delay) from an exponential decline at about this rate, the adequacy of the operative procedure might need to be reconsiderd.

SUMMARY AND CONCLUSIONS

1. In a patient with complete-on-partial biliary obstruction due to a fibrosing adenocarcinoma at the junction of the hepatic ducts, serial bilirubin estimations were carried out over a period of 20 months from the onset of complete blockage until shortly before death. The rise in the serum bilirubin after the obstruction became complete suggested that it was exponential in character. But abnormal bilirubin loading presumably resulting from the breakdown of transfused and extravasated red cells temporarily increased the gradient of the rise immediately after 2 separate surgical traumas. The ultimate level of the serum bilirubin probably depended upon the renal clearance of bilirubin and was approximately 30 mg. per cent.

2. Daily analysis of the biliary bilirubin in 17 patients relieved of obstructive jaundice showed its concentration to rise to very high levels 2 days after operation. At this time its mean concentration was nearly 4 times that observed 12 days later, when the normal volume flow of bile had been restored and the abnormal load of bilirubin resulting from the operation had been eliminated.

3. Following the operative relief of obstructive jaundice there is often a secondary rise in the level of the serum bilirubin concentration. This secondary rise occurs 2 to 3 days after the operation. It is very small compared with the postoperative increase in the bilirubin concentration of the bile itself, evidence, therefore, of the efficiency of the liver as a bilirubin eliminator.

4. After this secondary rise in the serum bilirubin, its concentration falls exponentially at such a rate that it reaches its half-value in about 17.4 days. This average curve of decay of the serum bilirubin may be used to forecast roughly when jaundice should clear if operative relief of biliary obstruction has been adequate.

We are deeply grateful to the late Dr. John Foley for intellectual contributions to this paper.

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AN APPRAISAL OF THE PATHOGENESIS OF PRIMARY CARCINOMA OF THE EXTRAHEPATIC BILIARY TRACT

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CLINICAL studies on the pathogenesis of gall-bladder and bile-duct cancer have revealed that such cancers are relatively rare, are frequently associated with gallstones, and often diffusely involve the biliary tract. Experimental data indicate that gallstones may have carcinogenic activity, that bile may contain a carcinogen of steroid type, and that gall-bladder cancer can be produced by methylcholanthrene, a compound which is chemically related to the bile steroids.

The purpose of this paper is to correlate the clinical and experimental findings in an effort to ascertain the current status of knowledge of the pathogenesis of carcinoma of the extrahepatic biliary tract. The discussion will be focused principally on the etiologic relationship of gallstones and biliary carcinogens to biliary tract cancer.

THE CARCINOGENIC EFFECTS OF GALLSTONES

Gallstones appear etiologically related to biliary tract cancer, for stones are associated with 70 to 90 per cent of gall-bladder cancers[2, 50] and 20 to 57 per cent of bile-duct cancers.[41, 52] This incidence is considerably greater than that of a comparable age group in the general population where gallstones are found in 15 to 20 per cent of individuals over 40 years of age.[10, 18] It has been estimated that cancer of the biliary tract will develop in about 10 per cent of individuals over 65 years of age who have symptomatic biliary tract disease.[28]

This seemingly causal relationship has been variously interpreted. It has been postulated that gallstones induce cancer either by chronic irritation of the biliary system or by the specific effects of a chemical carcinogen in the stones. However, some writers have suggested a modifying action on carcinogenesis by gallstones. Others believe that gallstones have no carcinogenic activity but are formed secondarily to the obstructive changes of biliary tract cancer, or the gallstones and the cancer are formed by the same undefined phenomena.

GALLSTONES AS CHRONIC IRRITANTS

The rather ambiguous term "chronic irritation by gallstones" might be defined as the repeated injury to or stimulation by gallstones of the gall-bladder

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wall with resultant inflammatory reaction. Early writers believed that gall-bladder cancer was caused by the chronic irritant effects of gallstones. Subsequent pathologic studies and elucidation of the effects of pure carcinogenic compounds established that the inflammatory response to mechanical or to nonspecific injury does not progress to cancer except in very unusual circumstances.[4, 5, 8]

Some experiments on gall-bladder carcinogenesis would seem to indicate that the gall-bladder's reaction to an enclosed foreign body constitutes an unusual instance in which cancer is produced by chronic irritation. That is, the gall-bladder's reaction to the chronic irritation of gallstones is a specific carcinogenic response, unique for this organ. To date, unequivocal evidence that cancer of the gall bladder has been produced by the irritation of a foreign body is lacking. The extensive proliferative changes incited by placing gallstones, pebbles, pitch, balls of tar mixed with cement, and other foreign bodies into the lumen of the gall bladder of guinea pigs has been interpreted, at times, as cancer.[38, 45] However, other investigators have been unable to produce cancer by similar experiments and the pathologic changes have been shown to resemble chronic cholecystitis or "cholecystitis glandularis proliferans" rather than cancer.[7, 9, 16, 17] These conclusions undoubtedly apply to the experiments in which gall-bladder cancer was presumably induced by the implantation of ordinary glass tubes containing radon into the gall bladder of guinea pigs.[54] In this study, cancer is present in some of the illustrated animals, but histologic proof is lacking that the gall bladder is the site of origin of the cancer.

GALLSTONES AND SPECIFIC CARCINOGENS

There has been a limited exploration of the hypothesis that gallstones contain a chemical which is carcinogenic for the biliary tract. Such a carcinogen could be a compound which is commonly found in gallstones (cholesterol or related substances) or one which is incorporated from bile during the stone formation. The theoretical basis for the existence in bile of a carcinogen and the carcinogenicity of cholesterol and related compounds will be discussed in a subsequent section.

The possibility that a carcinogen is present in gallstones which are associated with gall-bladder cancer has been tested by placing gallstones from one patient with cancer of the gall bladder into the gall bladder of 6 guinea pigs.[16] No cancers were found in a species of animal which is not susceptible to the induction of gall-bladder cancer by other methods. Extracts prepared from gallstones which were obtained from a case of gall-bladder cancer did not produce skin tumors in mice. Spectrographic examination of the extracts failed to reveal findings distinctive of the compounds for which search was made.[39] The presence of radium in gallstones obtained from patients with cancer of the gall bladder has been reported[43, 44] but not confirmed.[16, 27]

GALLSTONES AS MODIFYING CARCINOGENESIS

Although lacking a specific carcinogenic effect, gallstones might influence the devolpment of biliary tract cancer by acting as a nonspecific irritant. Experimental data indicate that nonspecific irritation may precipitate or promote

the growth of a cancer which has been initiated by a specific carcinogen. An example of this phenomenon is the finding that the continuous application of tars to the skin of rabbits induces a continuous succession of changes leading to cancer formation. Intermittent applications induce changes up to a certain point with each application. In the tar-free interval, cells already "prepared" to become cancerous may be provoked by some nonspecific irritant or trauma which precipitates them into progressive uncoordinated growth.[46, 58] A localization of carcinogenic activity by trauma has been demonstrated by the tendency for tar tumors in mice to be preferentially located at the edges of deep incisions.[15, 56] These findings suggest that gallstones might precipitate or hasten the development of cancer by injury to an area carcinogenetically prepared by some chemical agent. The localization of carcinogenic activity by gallstones would account for the incidence of gall-bladder cancer which is greater than that of the bile ducts. Since gallstones are more common in the female, a "promoting action" of gallstones could account for the preponderant incidence of gall-bladder cancer in this sex.

The production of chronic cholecystitis could be the only effect related to carcinogenesis which is induced by gallstones. Chronic cholecystitis may be a necessary pathologic state for the development of gall-bladder cancer since chronic cholecystitis almost invariably accompanies this type of cancer.[2, 36, 64] The occurrence of cancer of the gall bladder in the absence of gallstones in 10 to 30 per cent of cases could be accounted for by the development of chronic cholecystitis by means other than the effect of gallstones. This conforms with the finding of chronic cholecystitis without gallstones in about 20 per cent of individuals examined at necropsy.[10]

It is evident that application of the general effects of nonspecific irritants to gall-bladder carcinogenesis currently permits only speculation. The experimental results vary with the species of animal, the various tissues tested, the nonspecific irritant, and the carcinogen used, and whether the irritant is applied before, after, or concurrently with the carcinogen. Clarification of the effects of chronic irritation on gall-bladder carcinogenesis is indicated.

GALLSTONE FORMATION AND CANCER INDUCTION

Another explanation for the association of gallstones with biliary tract cancer is that the stones form secondarily to the obstructive changes of cancer in the biliary system or that both stones and the cancer are caused by the same phenomena.[35] Clinical data indicate that, in most instances, gall-bladder disease or cholelithiasis precedes the development of gall-bladder cancer. About 50 per cent of patients with cancer of the gall bladder, in many reported series,[13, 47, 64] have had symptoms of gall-bladder disease which antecede the clinical diagnosis of cancer by an average of 10 or more years. Additional patients will have had gallstones, without symptoms, for 50 to 60 per cent of gallstones found in some necropsy series have apparently caused no symptoms.[48, 57]

The type of gallstones associated with gall-bladder cancer is usually not the obstructive or calcium carbonate stone.[55] The stones most commonly associated with gall-bladder cancer are the solitary cholesterol or the mixed type

stones.[62] These stones probably are formed as a result of an alteration in the bile-salt-cholesterol-fatty acid ratio with resultant precipitation of cholesterol.[19, 37] Changes in this complex do not seem to be etiologically related to cancer induction. However, in some instances, a decrease in the level of bile salts as a result of secondary liver damage could cause alteration in the complex with formation of gallstones. The time required for gallstones to form may be brief, for relatively large and multiple, cholesterol-type gallstones are found in Syrian hamsters fed a fat-deficient diet for 17 days.[23, 24]

It must be concluded that any causal relationship which may exist between gallstones and biliary tract cancer has not yet been defined. Many interesting theories and possibilities have been presented since 1869, when it was first suggested that gallstones caused cancer of the gall bladder.[42] Little factual data have, however, been developed. The problem is made singularly complex by a considerable lack of knowledge concerning the cause of gallstone formation, the inherent difficulties of attempting to detect a carcinogen whose presence and nature are purely speculative, and the unawareness of the existence of an animal which is susceptible to the experimental induction of gall-bladder cancer. It is probable that a specific or nonspecific carcinogenic activity of gallstones on the gall bladder, if present, can be defined by the use of a satisfactory test animal.

THE EXPERIMENTAL INDUCTION OF GALL-BLADDER CANCER

Attempts to induce primary carcinoma of the gall bladder in rabbits and guinea pigs have been uniformly unsuccessful or equivocal. Recent studies have shown that the cat's gall bladder is susceptible to the induction of cancer by a compound chemically related to the bile steroids.[25] Primary carcinoma of the gall bladder with invasion of adjacent organs and with metastasis was found in 5 of 6 cats which survived 23 to 32 months after the implantation of a single pellet of methylcholanthrene in the lumen of their gall bladder. Histologically, the tumors were adenocarcinomas and adenosquamous carcinomas. Direct extension and invasion by tumor was observed in the liver, adjacent abdominal wall, duodenum, pylorus, and pancreas. Massive invasion of the anterior chest wall occurred in one animal. The more frequent sites of metastasis were the liver, peritoneum, and lymph nodes of the greater omentum. Generalized metastases were found in one cat. The pronounced lymphatic permeation seen in these animals is similar to the early and extensive lymphatic spread seen in gall-bladder cancer affecting humans.

This production of gall-bladder cancer in an animal high on the phylogenetic scale by a compound chemically related to biliary steroids forms a basis for studying various factors concerned with the etiology of biliary tract cancer in humans. Theoretic support for the hypothesis that biliary tract cancer is induced by a compound related to the biliary steroids is also attained.

THE CARCINOGENICITY OF BILE

The primary etiologic agent for biliary tract cancer may be a compound in bile which is carcinogenic for the biliary system. Theoretically, carcinogenic

activity could be manifested by abnormal metabolites of steroids excreted in bile or by compounds physiologically present in bile. Detection of such carcinogenic agents is uniquely possible for the posthepatic location of cancers of the extrahepatic biliary tract necessitates that the hypothetical chemical already has been subjected to the degradative activity of the liver and excreted in the bile as a carcinogenic agent. The theory of the in vivo formation of chemical carcinogens can be crucially tested.[26]

Abnormal Metabolites.—The chemical relationships of biliary steroids and carcinogenic hydrocarbons of phenanthrene type suggest that the chemical structure of some compounds naturally excreted in bile could be abnormally altered metabolically to produce carcinogenic hydrocarbons. The more suspected biliary steroids are cholesterol and the bile acids. Deoxycholic and cholic acid have a close structural resemblance to methylcholanthrene and related carcinogenic hydrocarbons. Methylcholanthrene has been prepared from cholic acid, deoxycholic acid, and from cholesterol by the type of chemical reactions which occur biologically.[11, 20] The susceptibility of the extrahepatic biliary tract epithelium to cancer induction by carcinogens related to naturally occurring compounds in bile is shown by the induction of gall-bladder cancer in cats by topically applied methylcholanthrene.[25] Failure to demonstrate the presence of compounds of methylcholanthrene type in cancerous tissues and in urine[22] does not exclude the possibility of the presence in bile of such compounds. It is also possible that carcinogenic transformation products of a natural steroid other than an aromatic hydrocarbon may have escaped attention (that is, cholesteryl isoheptylate, $\triangle^6$ cholestene-3-one, or oxidation products of lathosterol).[21]

The specificity of the hypothetical carcinogen for the biliary tract is suggested by the apparent immunity of the extrahepatic biliary tract to hepatic carcinogens in general and by the relative specificity of some groups of carcinogens. With few exceptions, the polycyclic hydrocarbons produce tumors at the site of application and the azo dyes and halogenated aliphatic hydrocarbons (carbon tetrachloride) produce liver tumors.[30]

The occurrence of the biliary excretion of carcinogens or their metabolic products has been demonstrated. Metabolic derivatives of dibenzanthracene[31] and p-dimethylaminoazobenzene[49] have been identified in bile. The intravenous administration of benzpyrene results in the excretion in bile of a blue fluorescent material (BPX), identified as a precursor of the phenolic derivative of benzpyrene.[53] The subcutaneous injection into mice of C^{15}-labelled methylcholanthrene resulted in the excretion of methylcholanthrene or its metabolic products principally in the feces, presumably via the bile.[14] Biologically, the presence in bile of an orally administered carcinogen or its carcinogenic derivative has been demonstrated. The feeding of o-aminoazotoluene to 2 dogs for 30 to 62 months resulted in the formation of adenocarcinomas which involved the entire biliary tract.[51] The lesions produced experimentally bear a resemblance to the diffuse involvement of the biliary tract by cancer in humans.[41, 61, 66]

Physiologic Carcinogens.—Some naturally occurring compounds in bile may be intrinsically carcinogenic or converted under certain local conditions to

compounds which are carcinogenic. Subcutaneous sarcomas in mice have been produced by the injection of deoxycholic acid[12] and of cholesterol.[32, 33] Liver tumors of bile-duct and hepatic cell type have been produced in hamsters by the administration of estrogens.[40]

BILE STUDIES

Experiments directly concerned with the possible carcinogenic activity of bile have been inconclusive. Most of these studies have dealt with agonal bile obtained at autopsy and are not representative of the bile normally excreted by the individual. Little attention has been given to the type of cancer with which the donor has been afflicted.

A benzene extract of gall-bladder bile obtained at autopsy from persons dead of gastric cancer, lung cancer, and sarcoma produced tumors in 23 per cent of surviving mice.[59] The nonsaponifiable fraction of the dried residue of gall bladder and gall-bladder bile produced 5 sarcomas in 53 mice when injected subcutaneously. About 40 per cent of the donor individuals had cancer.[60] The unsaponifiable fraction of human bile and gall bladders produced one sarcoma at the site of injection in 40 C-57 strain mice.[34] Ox gall, with and without estrin, was injected into 126 mice. One sarcoma was produced at the site of injection and the incidence of hepatomas in male C_3H mice was increased.[63] A leukemia-like picture was produced in mice with a dried bile solution after only a 4-week injection period.[6] The presence of a hypothetical chemical in bile, which is carcinogenic for the biliary tract, has not been demonstrated. Further evaluation of this problem is currently being carried out.

SUMMARY

The theory that cancer of the extrahepatic biliary tract is caused by a carcinogen in bile is inferentially supported by clinical studies and experimental findings. The theoretical bases for the existence of a carcinogen produced or excreted by the liver are: (1) the similarity in chemical structure of certain carcinogenic hydrocarbons and many naturally occurring steroids (that is, methylcholanthrene and the bile acids); (2) the in vitro conversion of cholesterol and deoxycholic and cholic acids to methylcholanthrene; (3) the numerous possibilities for aberrations to occur in the biogenesis of cholesterol, bile acids, and other steroids with resultant formation of carcinogenic compounds; (4) the carcinogenicity of cholesterol and bile acids for the subcutaneous tissues of the mouse and of estrogens for the liver of the hamster; and (5) the similarity between pathologic findings in cancer of the extrahepatic biliary tract in humans and those of experimentally induced cancers. The excretion in bile of a hypothetical carcinogen would be expected on the basis that the biliary route is a prominent means of excretion of many experimental carcinogens or their metabolites. The specific nature of the carcinogen is suggested by: (1) the apparent immunity of the extrahepatic biliary tract to most experimental hepatic carcinogens; (2) the relative specificity of some groups of carcinogens; (3) the production of gall-bladder cancer in the cat with methylcholanthrene and the failure

to produce gall-bladder cancer in the guinea pig by methylcholanthrene, dibenzanthracene, cholesterol, pitch, and tar; (4) the failure to demonstrate carcinogenic agents for most cancers occurring in humans; and (5) the relatively few reported instances of multiple primary cancers in humans in which one of the primary lesions has been the biliary tract.

The effect of gallstones on the induction of gall-bladder cancer may be either that of localizing or potentiating the effect of a biliary carcinogen. On the other hand, the possibility exists that gallstones may form subsequent to the initiation of the cancer. Any carcinogenic activity of gallstones or of bile should be detectable by the use of an experimental animal in which cancer of the gall bladder can be produced by a standard control method.

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STUDIES CONCERNING HEPATIC pH CHANGES AND SURVIVAL FOLLOWING TEMPORARY AFFERENT VASCULAR ARREST TO THE LIVER

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IN A discussion concerning partial hepatectomy for removal of tumor of the liver, it has been stated: "Safeguarding the patient against dangerous loss of blood during the removal of liver tumor constitutes by far the major problem of the entire procedure."[6] One of the major causes of death following traumatic lesions of the liver is shock resulting from uncontrolled hemorrhage.[7]

It is possible to reduce blood loss during operative procedures upon the liver by temporary occlusion of the portal vein and hepatic artery, but this maneuver is attended by a high mortality rate if extended over a period as long as one hour.[5] The exact cause of death following temporary arrest of the afferent hepatic circulation has not been established.[8] It has been shown that the pH of the liver drops rapidly following arrest of its circulation.[1] Abnormal degrees of acidity increase the likelihood of formation of miliary clots during circulatory stasis.[2] The following observations were concerned with the effects of pH changes in the liver upon survival of animals following periods of afferent circulatory arrest of one hour.

MATERIALS AND METHODS

Eighteen adult mongrel dogs were used for these studies. Anesthesia was induced by the intravenous administration of Nembutal. The upper abdomen and right groin were shaved and prepared with green soap and alcohol. Sterile technique was employed during all operative procedures. Following exposure of a segment of the femoral vein 3 cm. in length, an upper midline abdominal incision was made.

Measurement of Liver pH.—Liver pH determinations were obtained from a Photovolt direct reading, line-operated pH meter (accuracy of ± 0.05 pH units). Two electrodes were used, one of which was placed directly into the liver and the other into the peritoneal cavity. The latter was a calomel reference electrode. The former was a Beckman quinhydrone glass electrode constructed for tissue pH measurement. The tip was inserted into the right lobe of the liver to a depth of approximately one-fourth inch after it had been standardized with buffers ranging from pH 7.00 to 4.00. The pH apparatus was restandardized at regular intervals. Except during standardizations of the system the

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indicating electrode was allowed to remain in the liver throughout an entire experiment. The pH values were recorded at 15-minute intervals for the duration of each experiment.

Experimental Procedure.—Animals used for these studies were divided into the following groups.

Group 1 (5 animals): A pH value for the liver with normal circulation was first obtained. The portal vein near the hilum of the liver was then freed and a loop of 2-0 silk was loosely placed around it. The spleen was delivered into the wound and one of the splenic veins was dissected free. A temporary portacaval shunt was constructed by placing one end of a heparinized polyethylene tube in this vessel and the other end in the femoral vein. The portal vein was occluded for one hour during which time pH values were recorded at 15-minute intervals. Following release of the portal vein, the polyethylene tube was removed and the femoral and splenic veins were ligated. The abdominal wound was closed after the spleen had been replaced within the abdominal cavity.

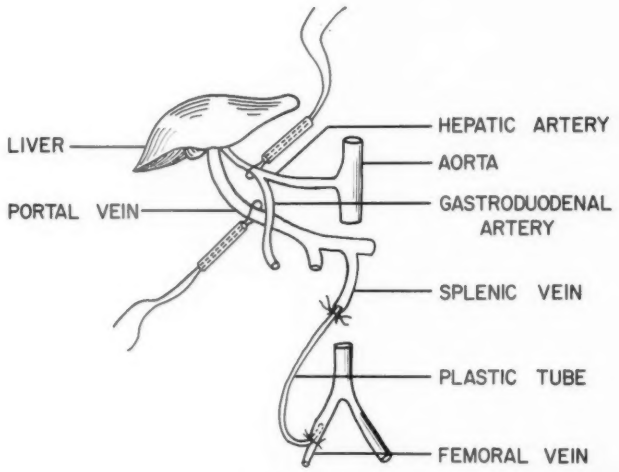

Fig. 1.—Method of arresting the afferent blood supply to the liver.

Group 2 (6 animals): Control liver pH values were recorded without alteration of the circulation. A temporary portacaval shunt was then constructed as described above. The portal vein and hepatic artery were occluded simultaneously (Fig. 1). For one hour pH values for the ischemic liver were recorded. Occlusion of the hepatic artery and portal vein was then terminated and the polyethylene tube was removed.

Group 3 (7 animals): The procedure was the same as for group 2 except that these animals received 600,000 units of penicillin when they were anesthetized.

RESULTS

Group 1.—The mean pH value after occlusion of the portal vein for one hour was 6.92 (range 6.90 to 6.95). All animals recovered and were active on the first postoperative day (Table I).

TABLE I. RESULTS IN ALL ANIMALS STUDIED

DOG NUMBER	PENICILLIN	HEPATIC ARTERY OCCLUDED	PORTAL VEIN OCCLUDED	RECOVERED
5	0	0	+	5
6	0	+	+	2
7	+	+	+	6

Group 2.—With normal circulation the mean value for the liver pH was 7.33. Following arrest of the afferent blood supply for one hour this reading dropped to 6.35 (Table II). After the elapse of 24 hours only 2 of the 6 animals were alive.

TABLE II. LIVER pH CHANGES FOLLOWING TEMPORARY OCCLUSION OF THE HEPATIC ARTERY AND PORTAL VEIN (NO PENICILLIN)

TIME (MIN.)	NORMAL CIRCULATION	CIRCULATORY ARREST			
		15	30	45	60
pH (mean)	7.33	6.94	6.69	6.54	6.35
Range	7.25	6.75	6.50	6.35	6.20
	7.40	7.18	6.85	6.70	6.50

Group 3.—Before arrest of the afferent blood supply the mean liver pH was found to be 7.35. One hour after occlusion of the hepatic artery and portal vein, this value was found to be 6.41 (Table III). Six of the 7 animals recovered.

TABLE III. LIVER pH CHANGES FOLLOWING TEMPORARY OCCLUSION OF THE HEPATIC ARTERY AND PORTAL VEIN (PENICILLIN GIVEN)

TIME (MIN.)	NORMAL CIRCULATION	CIRCULATORY ARREST			
		15	30	45	60
pH (mean)	7.35	6.99	6.66	6.57	6.41
Range	7.30	6.78	6.30	6.15	6.10
	7.43	7.20	6.99	6.95	6.65

Animals That Recovered.—Eight animals survived total afferent vascular arrest to the liver of one hour's duration. With normal hepatic circulation, the mean pH reading was 7.34. One hour after occlusion of the hepatic artery and portal vein, this value had changed to 6.42 (Table IV).

TABLE IV. LIVER pH VALUES IN ANIMALS THAT FAILED TO RECOVER

TIME (MIN.)	NORMAL CIRCULATION	CIRCULATORY ARREST			
		15	30	45	60
pH (mean)	7.34	6.97	6.68	6.47	6.32
Range	7.30	6.75	6.50	6.15	6.10
	7.40	7.19	6.83	6.60	6.50

Animals That Died.—Following hepatic ischemia which lasted for one hour 5 animals died. The mean control pH value for this group was 7.34. One hour after arrest of the afferent blood supply this figure was found to be 6.32 (Table V).

TABLE V. LIVER pH VALUES IN ANIMALS THAT RECOVERED

TIME (MIN.)	NORMAL CIRCULATION	CIRCULATORY ARREST			
		15	30	45	60
pH (mean)	7.34	6.97	6.68	6.62	6.42
Range	7.25	6.78	6.30	6.20	6.20
	7.43	7.20	6.99	6.95	6.65

COMMENT

In any procedure designed to determine the results of arrest of the afferent blood supply to the liver the effects of associated portal hypertension must be considered. Large amounts of blood are pooled in the splanchnic bed following occlusion of the portal vein.[4] The intestines become dark and congested in appearance. Occlusion of the arterial supply to the gastrointestinal tract is one method of overcoming portal congestion but the factor of ischemia of these organs is substituted. Arrest of the aorta above the celiac axis is attended by a rather high mortality.[3]

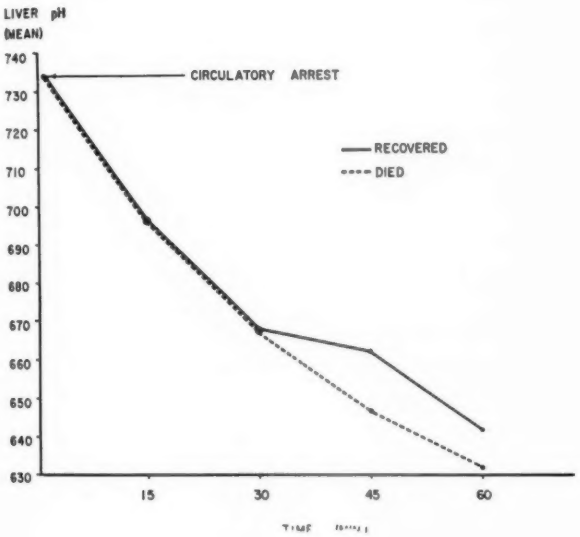

Fig. 2.

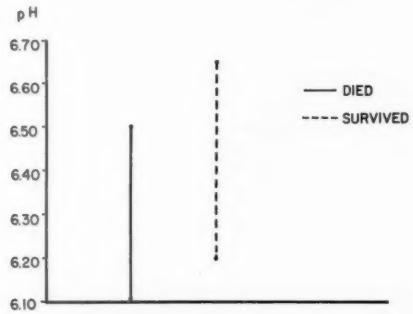

Fig. 3.

Fig. 2.—Comparison of mean pH values in survivors with those animals that died.
Fig. 3.—Comparison of pH range in survivors and those animals that died after afferent hepatic circulatory arrest for one hour.

In the first group of animals it was shown that an effective temporary portacaval shunt could be constructed by use of a polyethylene tube. The intestine remained pink and without evidence of venous congestion. At the conclusion of each period of portal vein occlusion, when the tube was removed from the splenic vein and elevated, the contained blood readily flowed into the femoral vein. After all animals of group 1 recovered following a one-hour period of occlusion of the portal vein, it was concluded that the complications of portal congestion had been sufficiently minimized.

The rate of decline in mean pH values during the first 30 minutes of afferent vascular occlusion was the same in animals that recovered as in those

that died. During the second 30-minute period the pH fell faster in those animals that died. The final reading after one hour was 0.10 pH units higher in the animals that recovered (Fig. 2). The overlap in pH range between the survivors and those that died was considerable (Fig. 3). All animals died that experienced a pH drop below 6.20 whereas all lived when the pH remained above 6.50. Most of the values were between these figures and consequently were of little aid in predicting the ultimate fate of the animal.

The survival rate was much better in those animals that received penicillin. Although the mean pH decline in this group was 6.41, one animal gave a reading of 6.10.

CONCLUSIONS

1. Occlusion of the portal vein for one hour was not fatal provided adequate drainage of the portal system was effected.

2. The administration of penicillin improved the survival rate in animals subjected to afferent circulatory arrest of the liver.

3. The mean pH value after arrest of the afferent liver circulation for one hour was 6.35 in animals that did not receive penicillin, 6.41 in animals that did receive penicillin, 6.32 in animals that died, and 6.42 in animals that recovered.

4. Using pH readings as a guide, we were unable to significantly predict which animal would survive.

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CAVERNOUS HEMANGIOMA OF THE LIVER

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IN THE liver, malformations of blood vessels are observed singly or occasionally in multiple foci. The pattern of the adjacent liver is usually undisturbed with no pressure phenomena evident. The malformations consist of blood-containing spaces bordered by narrow or broad connective tissue septa lined with endothelium. These structures are believed to be hamartomas (tissue malformations) rather than neoplasms (angiomas). Such so-called cavernous hemangiomas or vascular hamartomas are encountered at surgical operations and at necropsies. When these are of considerable size, they may produce clinical signs and symptoms. Cognizance of their existence should be taken since occasionally they have been misinterpreted. Their true incidence has never been investigated in a considerable number of individuals. The present study was undertaken to determine the incidence of vascular hamartomas and to restudy their gross and microscopic features.

MATERIAL AND METHOD

The necropsy records of the Veterans Administration Hospital, Houston, Tex., were surveyed for the period Oct. 1, 1949, through May 7, 1957. During this time 2,400 necropsies were performed on male veteran patients. Of these, 1,781 were white and 619 Negro. Vascular hamartomas in the liver were observed in 55 of the patients (32 white and 23 Negro). In most instances the liver was examined on frontal cut surfaces about 1 to 3 cm. apart. The location, size, and number of the hamartomas encountered were usually recorded. The nature of each was verified by microscopic examination.

OBSERVATIONS

Of the 55 patients with vascular hamartomas of the liver, 50 had only one hamartoma and the remaining 5 had 2 or more. The solitary hamartomas were located in the right lobe in 28 and in the left lobe in 13. The location was not accurately recorded in 9 instances. Of these solitary hamartomas, 29 were immediately beneath the surface, 4 were in the parenchyma of the liver, and the depth was not recorded in 17. The multiple hamartomas were located in both lobes in 4 instances and in the right lobe only in one. The multiple hamartomas were immediately beneath the capsule in 4 instances and the depth was not recorded in the fifth. None of the hamartomas were located in either the quadrate or the caudate lobes.

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The age distribution of all patients examined after death and of those with vascular hamartoma of the liver is given in Table I. There seems to be no predilection for any age group.

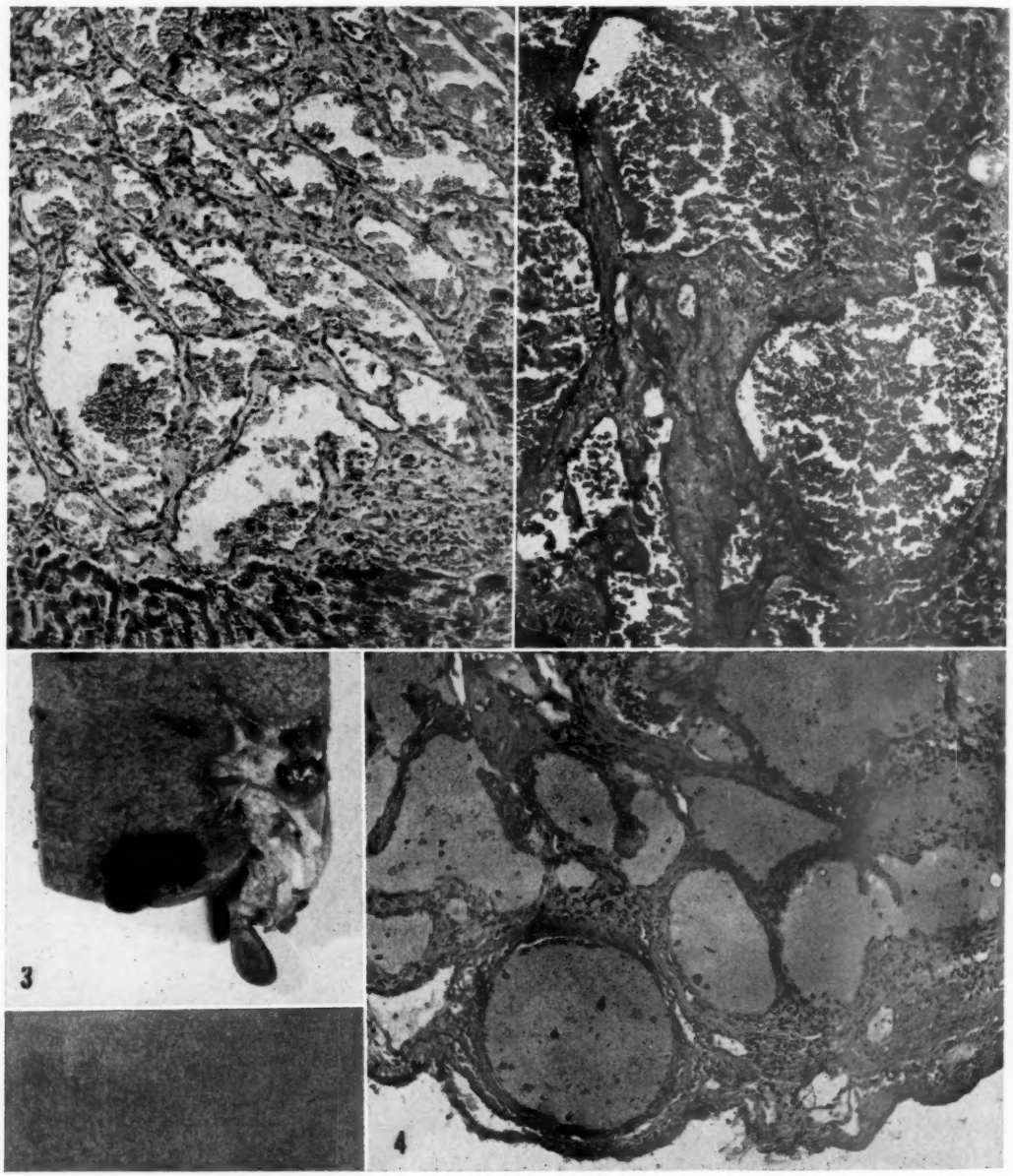

Fig. 1.—Microscopic appearance of a vascular hamartoma on the anterior surface of the liver in a white man, aged 63. Various sized angular blood spaces lined with endothelium are separated by connective tissue septa of varying widths. The border toward the liver parenchyma is unaltered with no pressure phenomena discernible. (×100, ⅛ off reduction.)

Fig. 2.—Microscopic appearance of a vascular hamartoma of the liver in a Negro man, aged 57. Broad septa separate the blood spaces that have no effect on the adjacent hepatic cell cords. (×100, ⅛ off reduction.)

Fig. 3.—Vascular hamartoma, 1.5 by 1 cm., near the posterior surface of the liver in a white man, aged 56. The sponge-like pattern contrasts with the light liver parenchyma. The surface beneath the capsule is slightly elevated.

Fig. 4.—Microscopic appearance of the vascular hamartoma shown in Fig. 3. The blood spaces are immediately beneath the capsule.

The gross appearance was dependent on size, location, and secondary changes (Figs. 3, 5, 7, 9, 11, and 13). On cut surfaces the hamartomas were angular, round, or oval. When they were close to the capsule of the liver, their surfaces appeared slightly depressed (Fig. 5), umbilicated (Fig. 7), or occasionally somewhat elevated (Fig. 3). The surrounding liver parenchyma was sharply demarcated. The sponge-like, purple-red pattern of the hamartoma contrasted with the hepatic pattern. The smallest was 0.4 cm. and the largest 8 cm. in diameter. Most of them were between 1 and 3 cm.

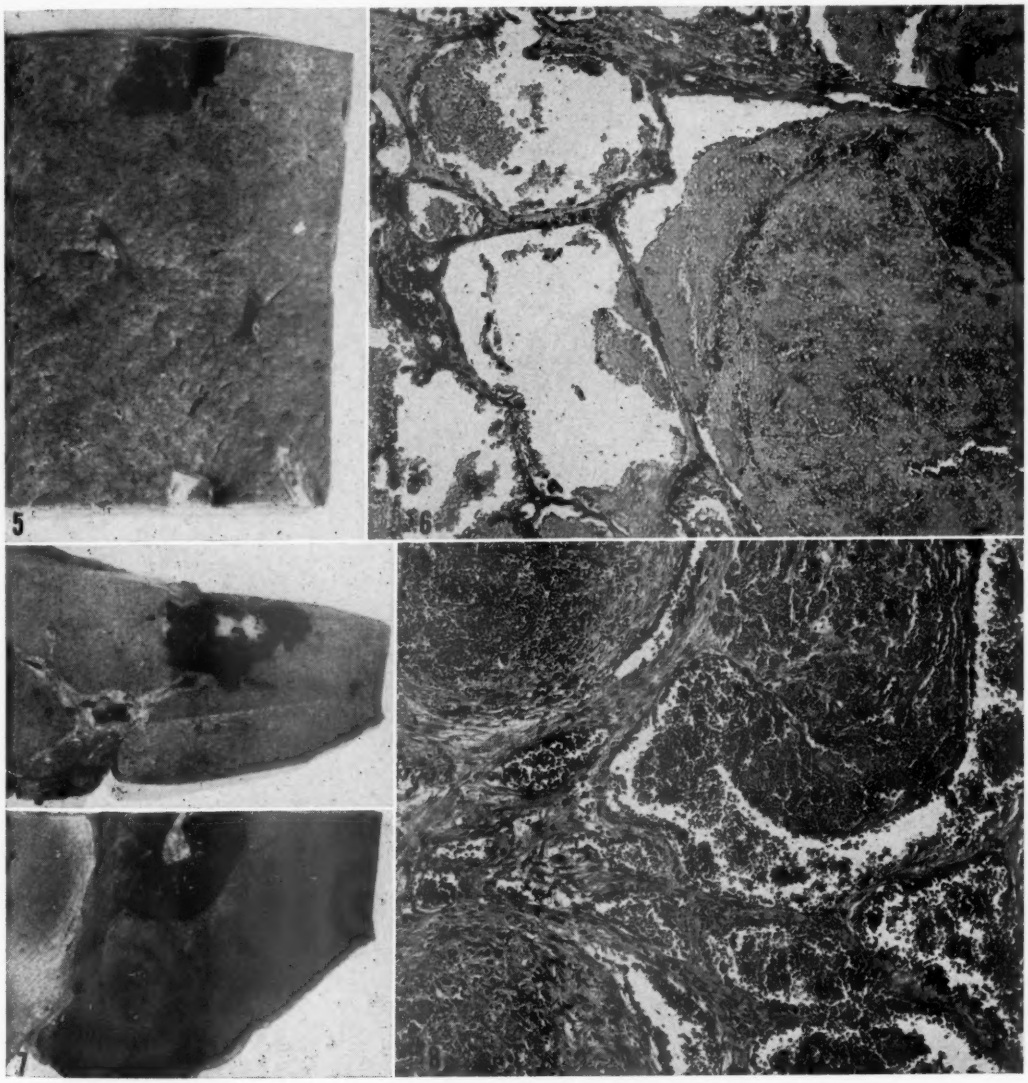

Fig. 5.—Vascular hamartoma, 1.5 by 1 cm., beneath the capsule of the liver in a white man, aged 39. The pattern is spongy with large spaces between delicate septa.

Fig. 6.—Microscopic appearance of the vascular hamartoma shown in Fig. 5. The content of a large space is filled with a recent thrombus. (×100, ⅛ off reduction.)

Fig. 7.—Vascular hamartoma, 2 by 1.5 cm., on the anterior surface of the left lobe of the liver near the falciform ligament in a white man, aged 60. There is a depression in the center of the protruding surface.

Fig. 8.—Microscopic appearance of the vascular hamartoma shown in Fig. 7. In some of the spacious blood spaces the content is clotted and in various stages of organization. (×100, ⅛ off reduction.)

The microscopic structure of all the vascular hamartomas was essentially alike. Various sized, angular spaces with broad or delicate, complete or incomplete, connective tissue septa were lined with endothelium. The spaces were filled with blood. In each hamartoma there were various sized blood spaces. Such variations were more marked in some of the hamartomas than in others. The border toward the liver parenchyma was smooth in parts; elsewhere the

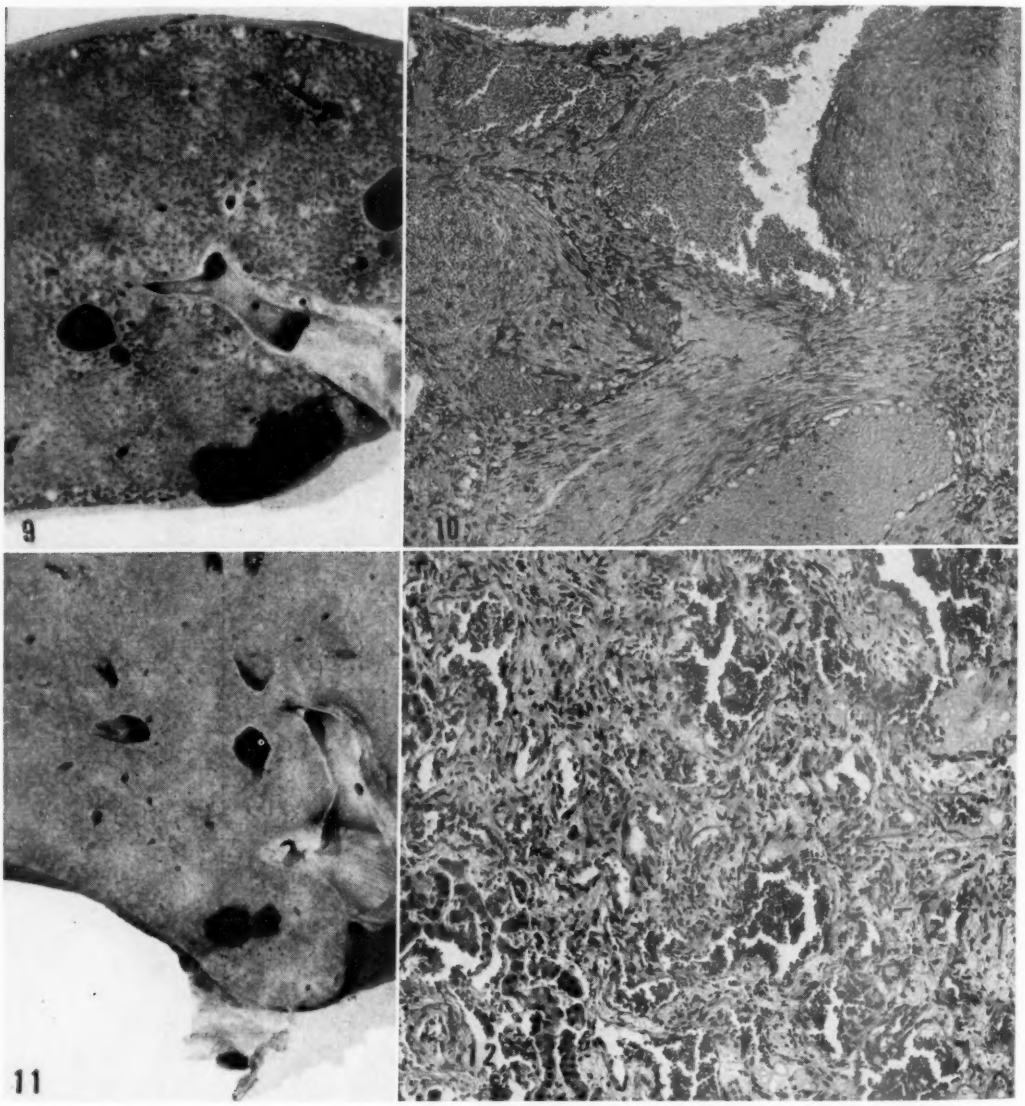

Fig. 9.—Vascular hamartoma on the posterior surface of the liver near the porta hepatis, 2.2 by 1 cm., in a white man, aged 32. There is marked chronic passive hyperemia of the liver. The patient had mitral stenosis.

Fig. 10.—Microscopic appearance of the hamartoma shown in Fig. 9. The blood content of some of the spaces is clotted with delicate fibrous connective tissue organizing the clot. (×100, ⅛ off reduction.)

Fig. 11.—Vascular hamartoma of the liver on its posterior surface near the porta hepatis, 1 by 0.5 cm., from a white man, aged 57.

Fig. 12.—Microscopic appearance of the vascular hamartoma shown in Fig. 11. At the margin toward the liver there is fibrous connective tissue replacement of some of the blood spaces with the septa of the remaining ones broad. (×100, ⅛ off reduction.)

TABLE I. AGE INCIDENCE OF VASCULAR HAMARTOMAS AMONG 2,400 PATIENTS EXAMINED AFTER DEATH

AGE (YEARS)	PATIENTS			VASCULAR HAMARTOMAS		
	TOTAL	WHITE	NEGRO	TOTAL	WHITE	NEGRO
Unknown	4	1	3	–		
Under 30	166	130	36	1	1	0
31-40	301	217	84	8	6	2
41-50	291	217	74	5	4	1
51-60	741	558	183	25	12	13
61-70	745	514	231	16	9	7
71 and over	152	144	8	–		
Total	2,400	1,781	619	55	32	23

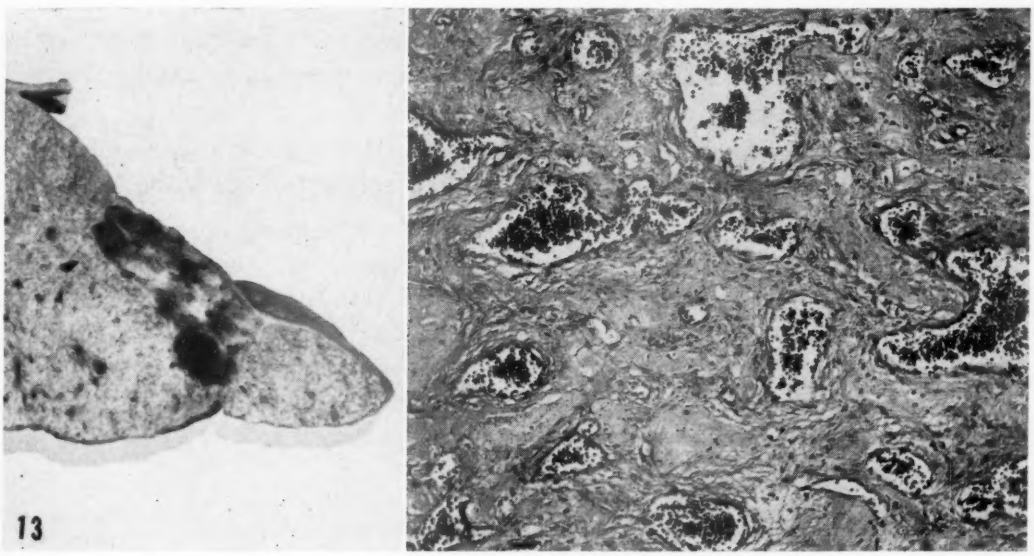

Fig. 13.—Vascular hamartoma, 2.8 by 0.5 cm., on the anterior surface of the left lobe of the liver in a 60-year-old Negro man who had portal cirrhosis. The cut surfaces are mottled with white areas interspersed.

Fig. 14.—Microscopic appearance of the vascular hamartoma shown in Fig. 13. Many of the blood spaces are replaced by hyalinized fibrous connective tissue. (×100, ⅛ off reduction.)

line was jagged with liver cell cords or lobules situated between adjacent blood spaces. An occasional space was surrounded by adjacent liver lobules (Figs. 1 and 2). No distortion or compression of either the hepatic or the vascular structures was noted about any of the vascular hamartomas. Secondary changes were often encountered. These ranged from recent clotting with slight lamination of the content to complete hyalin change of the coagulum and loss of pattern. Focal fields of hyalin change were common and varied from minute size to a substantial part of the hamartoma (Figs. 4, 6, 8, 10, 12, and 14).

Cysts of the liver were recorded in 4 instances. No consistent significant association with any disease or malformation was detected.

COMMENT

A detailed study of the structure and origin of 32 cases of cavernous hemangioma of the liver was reported by Schmieden in 1900.[6] He pointed out

the salient gross and microscopic features and concluded that these structures were malformations rather than neoplasms or the result of retrogressive changes.

The only statistical information as to the frequency of cavernous hemangioma of the liver is that of Adami[1] who recorded 20 instances in 1,400 necropsies. In our series of 2,400 necropsies the incidence was considerably higher.

Vascular hamartomas of the liver have been mistaken at operation for infarcts, nodular hyperplasia, hydatid cysts, and metastatic carcinoma.[3, 5] It has been suggested that all nodules in the liver encountered at operation should be biopsied. Hemangiomas of the liver have been diagnosed by percutaneous needle biopsy without incident; however, there is a real possibility of fatal hemorrhage from such lesions when located on the surface of the liver. When the surgeon is confronted at operation with one of these vascular hamartomas, sectioning or aspiration should not be attempted unless he is ready to resect the mass if considerable hemorrhage ensues.

Vascular hamartomas of the liver appear to have no growth potential. They often undergo retrogressive changes when there is interference with their circulation.

SUMMARY

Cavernous hemangiomas of the liver are in fact tissue malformations, vascular hamartomas. Their frequency in 2,400 necropsies was over 2 per cent. They were more often single than multiple and were more often near the surface of the liver than deep in the parenchyma. They appear to have no growth potential and are prone to undergo retrogressive changes that range from recent thrombosis to organization and hyalin change.

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EXPERIMENTAL STUDIES ON BLOOD PEPSINOGEN

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INTRODUCTION

PEPSINOGEN, the precursor of the gastric enzyme pepsin,[35] is present in both blood and urine. This fact has been known for many years.[4] However, attempts to define accurately the relationship of blood and urinary pepsinogen levels to gastric function have been recorded chiefly during the past decade. At present considerable literature exists on the subject.

The methods most commonly used to measure pepsinogen concentrations are modifications of the technique described by Anson and Mirsky[1] for the measurement of pepsin. Pepsinogen is autocatalytically broken down to pepsin in an acid medium (pH of 1.5 to 2.0). The amount of tyrosine and "tyrosine-like substances" subsequently split off during the digestion of a standard protein substrate (usually hemoglobin) is measured photoelectrically, and recorded as "tyrosine units" per milliliter.

Mirsky and co-workers[32, 34] have demonstrated the proteolytic activity of blood and urine at this pH to be chiefly due to pepsinogen. They have also shown serum pepsinogen to be excreted by the kidneys as urinary pepsinogen (uropepsin). This same group has offered the concept of the stomach as an exocrine-endocrine organ in so far as a fraction of the pepsinogen elaborated enters the blood stream. This exocrine-endocrine ratio appears to be fairly constant with the larger portion being delivered to the gastric lumen.[19, 26] This being so, it is to be expected that the pepsinogen levels found in blood and urine will mirror, to some extent, gastric function in health and disease. The potentialities for clinical use are provocative.

The greatest amount of clinical data has been collected by correlating urine pepsinogen levels with peptic ulcer disease. Thus it has been shown that duodenal ulcer patients, as a group, have higher than normal values. However, the overlap between ulcer patients and normal individuals is sufficiently large to prevent the assumption of more than confirmatory diagnostic evidence. It is the opinion of some that urine pepsinogen determinations are without routine clinical value in the diagnosis of peptic ulcer.[3, 13, 16, 22, 25] The reader

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is also referred to Gray,[18] and to Sircus,[37] for more optimistic evaluation of this test, with consideration of conditions both clinical and investigative in which it may be of use.

More recently, several groups have reported findings using blood pepsinogen measurements.[6, 24, 33, 34, 38] The findings have essentially paralleled those obtained by the measurement of urine pepsinogen. However, the determination of the enzyme in the blood appears to offer greater reproducibility and convenience.[24] This is especially true in animal experimentation when it may be difficult to make urine collections. For these reasons the latter method has been used in this study on the physiology of pepsinogen.

PURPOSE AND METHODS

We have attempted to assess the factors controlling blood pepsinogen levels and to study the relationship of blood pepsinogen levels to gastric secretory activity. Two approaches to this problem were used.

First, we have studied the fate of pepsinogen after its secretion into the circulation. It is obvious that the method and rate of excretion are as important as the rate of production in maintaining blood levels of pepsinogen.

Second, observations have been made on the degree to which blood pepsinogen levels vary in response to factors which act to modify gastric secretory activity.

All studies were carried out on mongrel dogs of either sex, weighing from 8 to 16 Kg. Intravenous pentobarbital sodium (Nembutal) anesthesia, 30 mg. per kilogram, was used routinely except for open chest procedures or bilateral nephrectomy in which cases ether was administered by a positive pressure pump following Pentothal induction. Aseptic technique was used routinely unless the animal was to be sacrificed in the end of the procedure. A single injection of streptomycin with long-acting penicillin* was given prior to operation for animals undergoing open anastomotic or transthoracic surgery.

Blood pepsinogen studies were done as described by Mirsky.[34]† Urine pepsinogen was determined by the method described by Gray.[18] Both of these methods are modifications of the original technique of Anson and Mirsky[1] used for the assay of pepsin. Usually serum, but occasionally plasma, was used for the determination of blood pepsinogen levels. Careful checks revealed no differences between the 2 fractions, a finding also reported by Chinn.[6]

RESULTS

Fate of Circulating Pepsinogen.—The stomach is the only source of pepsinogen entering the blood stream, as evidenced by a ~~marked~~ fall in blood

*Bicillimycin kindly supplied by Wyeth Laboratories, Philadelphia.

†Hoar and Browning[24] have recently described in detail this method of blood pepsinogen determination as performed in our laboratory, as well as an analysis of the reproducibility and variation for human and animal subjects. The determination was shown to be accurate and reproducible. The average coefficient of variation inherent in the procedure is 4 per cent. The average coefficient of variability from hour to hour and day to day is approximately 10 per cent with a mean normal value for humans of 486 tyrosine units (S.D. ±163). The normal mean value for (unanesthetized) dogs is 429 tyrosine units. Values after the induction of anesthesia tend to be somewhat lower. Changes of 50 units during acute experiments may be considered as significant.

and urinary levels for both man and experimental animals after total gastrectomy.[5, 18, 24, 37] Similar observations were made on a number of dogs undergoing total transthoracic gastrectomy during the present study. It is of interest that blood pepsinogen values do not fall to zero after total gastrectomy since an extragastric proteolytic fraction persists to act at the pH utilized in testing for pepsinogen. This fraction appears to remain at a relatively constant level of less than 100 tyrosine units per milliliter and has been considered to be catheptic in origin.[34] As will be pointed out later, this extragastric enzymatic fraction can be distinguished from pepsinogen both biologically and chemically.

Mirsky and his co-workers[32] have shown that pepsinogen, but not pepsin, is excreted by the kidney. In their experiments, pepsinogen injected into the blood stream of a dog gave a subsequent rise in urine pepsinogen levels. No elevation was seen after the administration of pepsin. Other investigators had previously shown the importance of the kidneys in pepsinogen excretion by demonstrating a rise in blood pepsinogen levels in dogs after bilateral ureteral ligation.[29]

In the present study bilateral nephrectomy was utilized in evaluating further the role of the kidney in pepsinogen excretion. Normal dogs were subjected, during a single operative procedure, to complete bilateral nephrectomy. The animals were maintained by the use of small amounts (50 to 100 ml. per day) of hypertonic glucose given intravenously, following the collection of blood samples. The results of 2 such experiments are plotted in the upper part of Fig. 1. Blood pepsinogen levels are seen to rise sharply postnephrectomy with a subsequent tendency to stabilize at a higher level.

Two animals which had previously undergone total gastrectomy were similarly subjected to bilateral nephrectomy. The results of this experiment are indicated in the lower portion of Fig. 1. These 2 animals, incapable of synthesizing pepsinogen, demonstrate the presence of the previously mentioned extragastric enzyme system (cathepsin) which also reacts at the low pH utilized in testing for pepsinogen. It will be noted that nephrectomy has no significant effect on the level of this enzyme.

The function of the kidney in pepsinogen excretion can be clearly demonstrated by using a cross-circulation preparation. Fig. 2 represents such an experiment. Cross-circulation using No. 190 polyethylene tubing was carried out for a 2-hour period between a previously gastrectomized dog and one which had undergone bilateral nephrectomy 4 days previously. Thus, the latter animal with a high blood pepsinogen level served as a donor of species specific pepsinogen for a recipient dog incapable of synthesizing the enzyme. Hourly urine collections were made from the recipient animal with intact kidneys and the urinary pepsinogen levels were calculated. During the first hour of cross-circulation there is a marked rise in the amount of urine pepsinogen excreted. Simultaneously, the donor's blood pepsinogen level is noted to fall, with a reciprocal rise of the recipient's blood enzyme level. The significance of these findings is considered below.

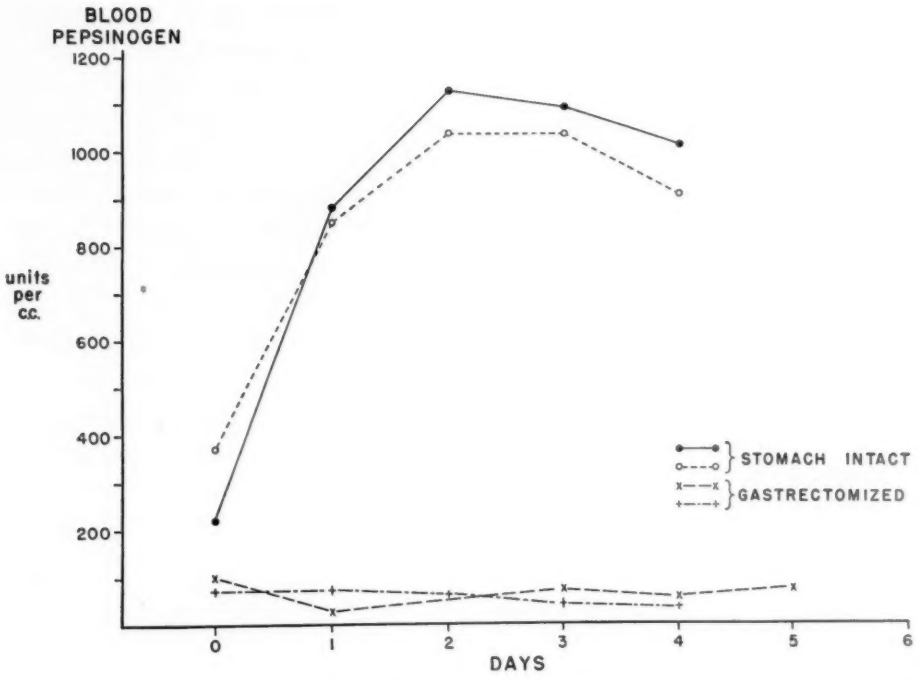

Fig. 1.—The effect of bilateral nephrectomy on normal and previously gastrectomized dogs. Nephrectomy was performed immediately after the initial value for each animal.

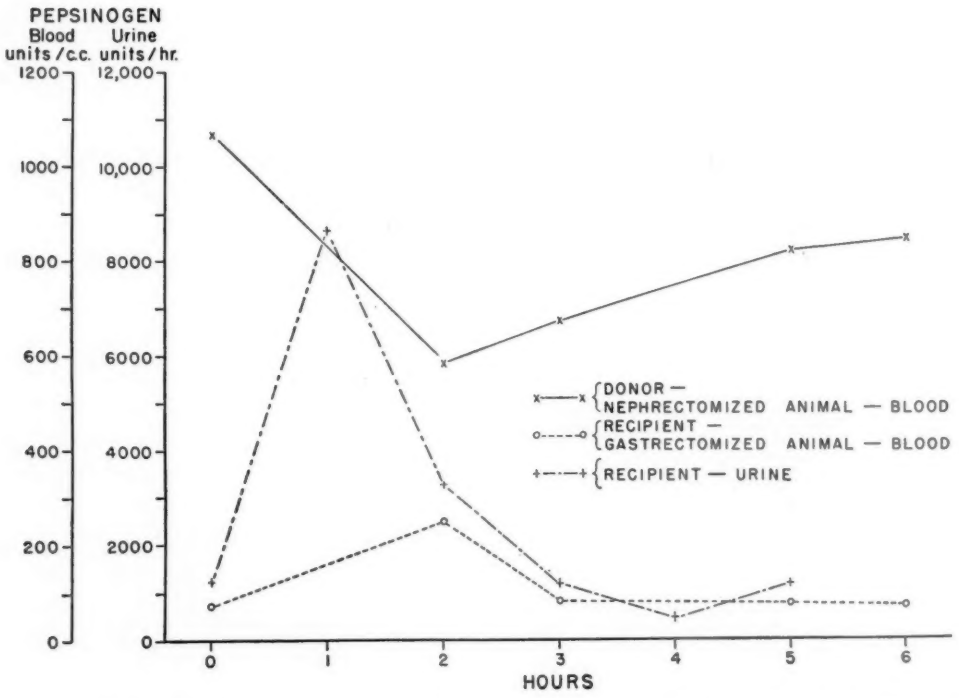

Fig. 2.—The effect of cross-circulation between a previously gastrectomized dog and an animal which had undergone bilateral nephrectomy 4 days previously. The latter animal serves as a donor of pepsinogen to an animal with no circulating enzyme.

Effect of Induced Changes in Gastric Secretory Activity on Blood Pepsinogen Levels.—

Mecholyl: Because of its role in normal gastric physiology, acetylcholine or its more stable derivative acetyl-β-methylcholine (Mecholyl) seemed to be an ideal agent for the evaluation of the response of blood pepsinogen to gastric stimulation. Gray and Ivy[17] have shown a maximum effect on gastric secretion in dogs following the administration of 0.1 mg. of Mecholyl subcutaneously every 10 minutes. Four dogs were studied during the present experiments using dosages in this range. Blood pepsinogen levels were determined in femoral venous blood. As indicated in Fig. 3, a significant elevation was seen in only 2 of these 4 animals. However, by making use of blood collected from a polyethylene cannula placed in a gastrosplenic vein (these veins drain the greater curvature of the dog's stomach to enter the splenic vein near the hilum of the spleen), it is possible to show a marked rise in blood pepsinogen levels. Such an experiment is also indicated in Fig. 3.

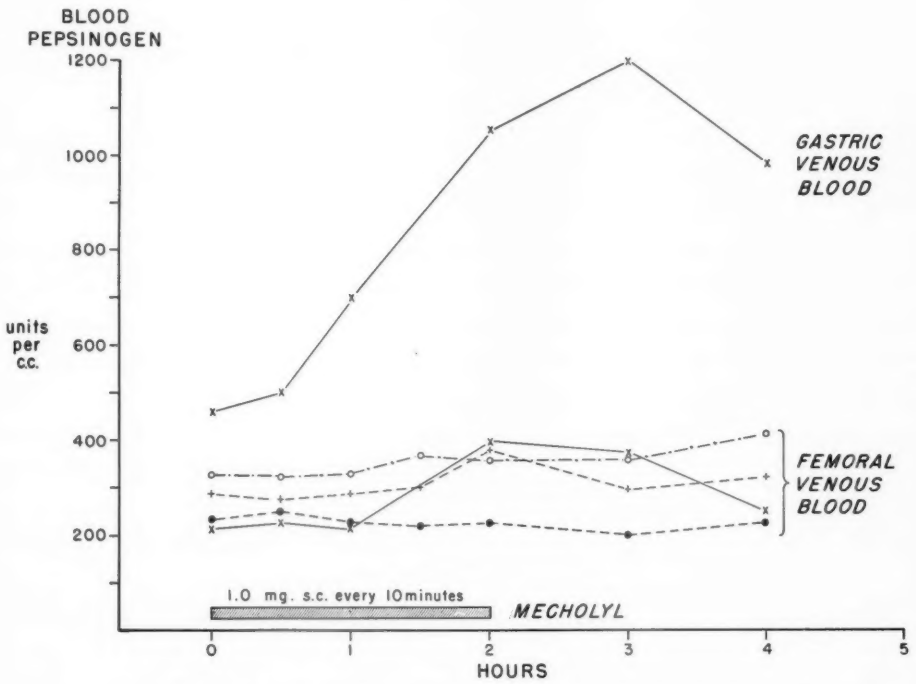

Fig. 3.—The effect of Mecholyl on blood pepsinogen concentrations.

ACTH: An attempt was made to demonstrate elevation of blood pepsinogen values in the peripheral blood of 3 dogs receiving daily injections of 40 units of ACTH gel intramuscularly. No significant elevation was seen. It is possible, however, to demonstrate an increase in pepsinogen levels in the gastric veins of animals receiving ACTH. Five normal dogs were prepared so that serial samples of blood could be obtained from a gastrosplenic vein via a polyethylene cannula. Simultaneous samples were taken from a femoral vein. ACTH was

administered intravenously in normal saline at the rate of 5 units per hour over 4 to 6 hours. Three control animals receiving similar amounts (200 ml.) of normal saline over the same period of time showed no significant change in pepsinogen levels in either gastric or femoral blood. However, all of the animals receiving ACTH demonstrated a significant elevation of blood pepsinogen in the gastric blood (Fig. 4). Note should be made that there was no appreciable rise of pepsinogen in the femoral vein blood during these experiments. The significance of this is considered in the discussion below.

Histamine: Three animals were given 30 mg. per day of histamine in beeswax as described by Hay and co-workers.[21] Two of these animals died of perforated peptic ulcer. The remaining animal survived 4 weeks of such chronic stimulation. In none was an unequivocal elevation of blood pepsinogen seen. We have found that it is necessary to give relatively massive dosages of histamine to produce significant elevation of blood pepsinogen levels (Fig. 5). Four dogs were given 75 mg. per Kilogram of histamine intramuscularly. A short time previously 3 of the animals had been given from 15 to 30 mg. per Kilogram of promethazine hydrochloride* intramuscularly to forestall systemic histamine effect. All of the animals showed marked elevation of peripheral circulating pepsinogen following histamine administration. Although all of the dogs died during the course of the experiment, the 2 animals receiving the largest amounts of this drug survived longer and developed elevation of pepsinogen levels later than did the 2 remaining animals.

Effect of various operative procedures on blood pepsinogen: As noted previously, both blood and urinary pepsinogen universally fall to low levels in both animal and man after total gastrectomy. This observation was repeated for a number of dogs undergoing gastrectomy during the present study.

During the course of these and other experiments a number of animals have been subjected to transthoracic bilateral vagotomy, usually coupled with some manner of pyloroplasty. Blood pepsinogen levels invariably have showed a significant drop postoperatively in every animal observed. In a series of 10 dogs the mean control value before vagotomy was 395 and postvagotomy 205 with an average difference for this group of 190 tyrosine units.

Various operations have been described which are productive of duodenal ulceration in dogs. Dragstedt has utilized a preparation in which the gastric antrum is transplanted to the colon.[11] In this way the antrum is stimulated more or less constantly by fecal stream. Thus, in theory, an abnormal amount of the antral hormone, gastrin, is secreted with a resultant hyperfunction of the remaining stomach. This operation was performed successfully on 11 dogs during the present study. Various types of gastroduodenostomy were used to re-establish gastrointestinal continuity. Dragstedt demonstrated ulceration in approximately 20 per cent of such preparations. In our series one animal died following acute perforation of a duodenal ulcer. In a second animal, scarring

*Phenergan kindly supplied by Wyeth Laboratories, Philadelphia, for use in these experiments.

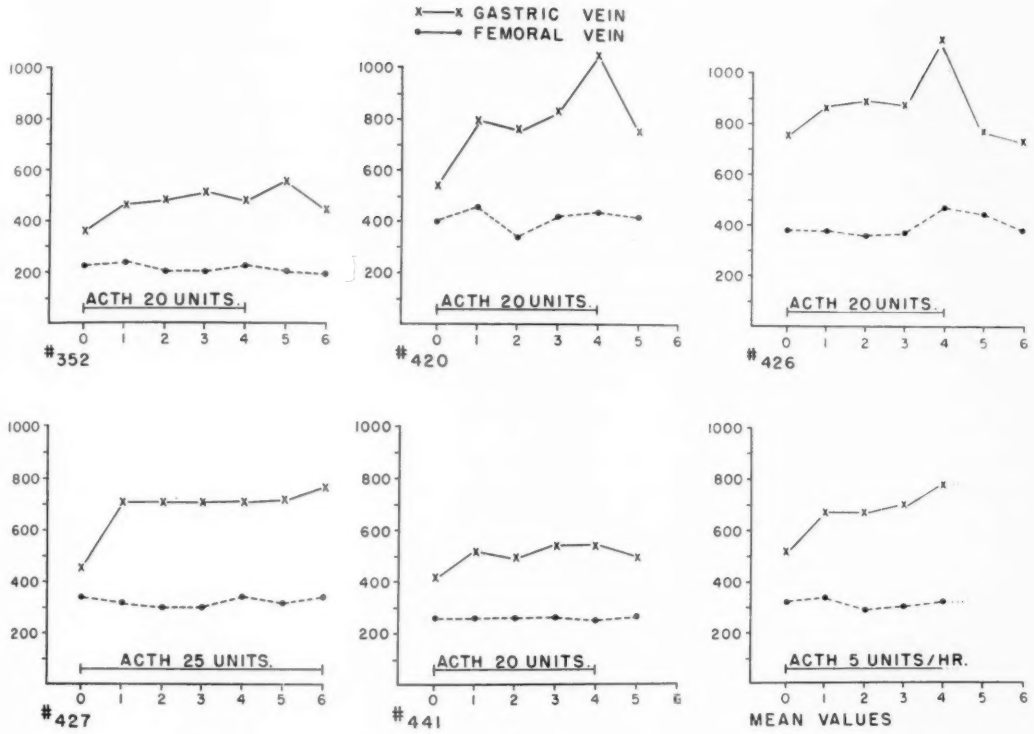

Fig. 4.—The effect of ACTH infusion on blood pepsinogen concentrations.

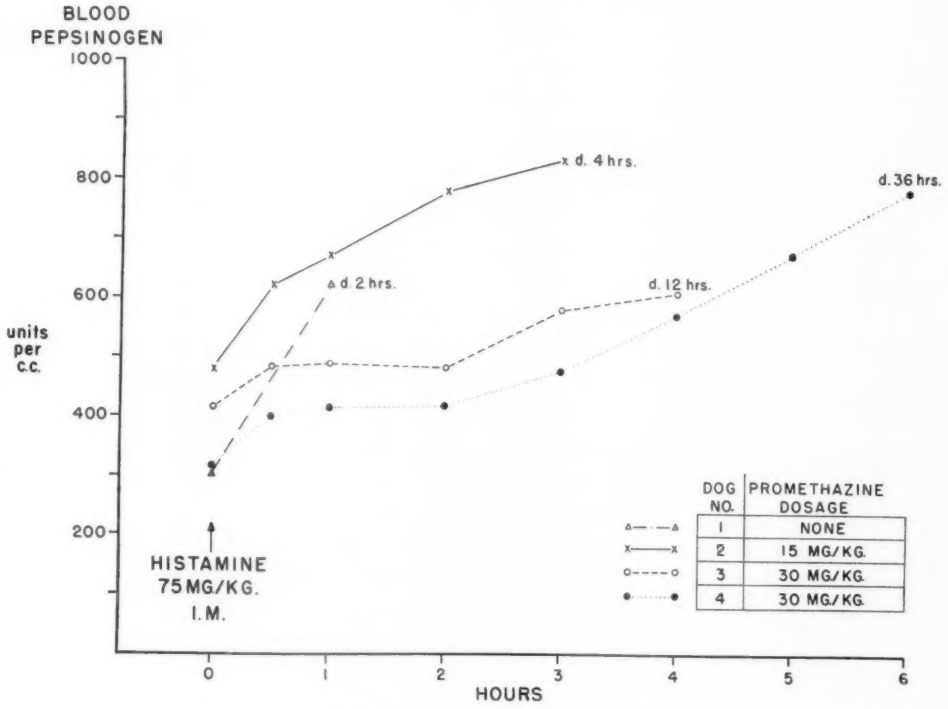

Fig. 5.—The effect of histamine on blood pepsinogen concentrations.

of the duodenum consistent with healed ulcer was noted at a subsequent operation. In none of these animals, including those with ulcers, was an elevated blood pepsinogen level noted postoperatively.

Three dogs were followed after Mann-Williamson duodenoileostomies.[30] Animals subjected to this operation notoriously do very poorly from the viewpoint of nutrition. Our preparations were no exception. The results were equivocal in that only one of the animals showed a suggestion of increased blood pepsinogen levels between operation and death.

DISCUSSION

The bilateral nephrectomy and cross-circulation animal preparations described demonstrate the importance of the kidney in the prompt excretion of circulating pepsinogen. This organ apparently is the only means by which pepsinogen is removed from the circulation in the normal animal. It is thus predictable that blood pepsinogen levels will be elevated clinically in patients with impaired renal function. We have noted in humans with uremia that circulating pepsinogen concentrations are often elevated, sometimes to a marked degree.[12] This observation is analogous to that of the elevation of pancreatic amylase levels in the presence of kidney failure, a phenomenon studied recently by Meroney and associates.[31] These investigators reported an increase in the serum amylase levels of dogs subsequent to acute renal impairment. These abnormal concentrations were essentially unchanged by dialysis on an artificial kidney. Similarly, we have noted that pepsinogen levels have not been significantly changed after dialysis in 2 patients in renal failure.[12] It is obvious that the presence of renal impairment must be recognized in the clinical interpretation of values dependent upon circulating proteolytic enzymes.

The comparison of gastrectomized with nongastrectomized dogs undergoing subsequent nephrectomy permits biologic differentiation between blood pepsinogen and the so-called catheptic fraction which also exerts proteolytic activity at pH 1.5 It is apparent that pepsinogen alone of these 2 enzyme systems is excreted by the kidney. This finding serves as biologic confirmation for the chemical differentiation of the 2 circulating enzyme systems which are active at a low pH, as reported by Mirsky and co-workers.[34]

Acetylcholine is of importance in the regulation of normal gastric secretion and has been demonstrated to be present in gastric venous blood following vagal stimulation.[9] There is evidence that acetylcholine acts chiefly on pepsin secretion with less effect on HCl production until higher concentrations are utilized. The physiology of acteylcholine, its derivatives, and their effects on the stomach have been extensively reviewed by Babkin.[2] Mecholyl as a stable derivative of acetylcholine represents an ideal substance to use in evaluating the response of blood pepsinogen levels to a known peptic secretagogue. As might be predicted, pepsinogen levels are elevated following the administration of Mecholyl to the experimental animal, a finding most marked in the gastric venous blood.

ACTH is also a physiologically active substance which appears to play a significant role in the regulation of gastric secretion. The clinical evidence for this conclusion is most persuasive and has been well summarized by Gray and

co-workers.[19, 20] Similarly, considerable experimental evidence is now available which demonstrates that ACTH is capable of producing gastric hypersecretion. Gray and associates[19] have shown the ability of ACTH to produce elevation of both gastric pepsin and urinary pepsinogen levels. Other investigators have also demonstrated clinically increased urinary pepsinogen excretion after ACTH administration.[8, 13, 15, 23] Villareal and co-workers[39] using animal pouch preparations have shown prompt increase in both gastric acidity and pepsin after ACTH injection. Similarly Gerity and associates,[14] Sigel and co-workers,[36] and Zubiran and co-workers,[40] have demonstrated increased gastric secretion following ACTH administration to animals. Kowalewski and colleagues[28] have reported the elevation of blood pepsinogen levels in dogs after the subcutaneous administration of ACTH. Hoar and Browning in a report from this laboratory,[24] further confirmed in the present report, describe the prompt elevation of pepsinogen in the gastric venous blood of dogs after ACTH administration.

The technique described of measuring pepsinogen levels in gastric venous blood appears to be a very sensitive method of bioassay, serving to detect changes in gastric peptic activity and allowing prerenal estimation of such changes.

Despite the consistent elevation seen in blood pepsinogen concentrations in gastric venous blood during our studies, we were at no time able to demonstrate an increase in enzyme levels in the peripheral circulation after ACTH administration. A parallel observation is that an elevation of blood pepsinogen has not been noted following the clinical use of ACTH or cortisone in humans.[24] This finding is unexpected even allowing for the obvious factor of peripheral dilution. An additional explanation may lie in the assumption that renal pepsinogen clearance is altered during ACTH administration. Davis and Howell[10] have demonstrated increased renal plasma flow and glomerular filtration rate shortly after the administration of ACTH to dogs. Thus, increased rate of pepsinogen excretion during ACTH administration may be acting to decrease the level of enzyme in the peripheral circulation and may cancel to some extent the effects of increased pepsinogen production induced during ACTH stimulation.

Histamine is well known as a potent gastric secretagogue. It appears that histamine also plays a definite part in the physiologic control of gastric secretion. Code[7] states: "Histamine is the final common local chemostimulator of the parietal cells of the gastric mucosa." As implied by this statement the principal action of histamine is to stimulate the secretion of hydrochloric acid, and as has been shown by others there is probably little primary effect on pepsin secretion.[2] Presumably it is for these reasons that the usual chronic ulcerogenic dosages of histamine cause no significant sustained elevation in blood pepsinogen levels; massive amounts of the drug are necessary to produce such a change. Kowalewski[27] has previously demonstrated that similar massive doses of histamine administered to guinea pigs are effective in elevating circulating pepsinogen levels. These findings are of questionable significance, however, because of the unphysiologic dosages employed.

To date we have been unable to produce consistently elevated blood pepsinogen levels in dogs using various ulcerogenic operative preparations, including the Dragstedt antral transplant. Gastrin has been shown, like histamine, to exert a direct action upon the acid-secreting parietal cell.[2] Thus, the observation that blood pepsinogen levels are not elevated in dogs with antral transplants is not an unexpected one. Rather, these findings accentuate the complexity of the control of gastric secretions, wherein acid and pepsin secretion may differentially respond to various stimuli, the presence of both substances being necessary for the peptic activity of the gastric juice. Changes in blood pepsinogen levels apparently follow changes in pepsin secretion and thus may be expected to serve as a guide to gastric secretory activity, particularly when this fraction of the gastric juice is altered.

During this and subsequent studies we have been impressed with the constancy and degree to which blood pepsinogen levels fall in the dog after vagotomy. These observations suggest that the determination of blood pepsinogen levels pre- and postvagotomy may be of assistance clinically in assessing the completeness of vagisection.

SUMMARY AND CONCLUSIONS

1. Factors influencing the production and excretion of circulating pepsinogen, the precursor of the gastric enzyme pepsin, have been studied.

2. Pepsinogen is excreted by the kidney, which acts promptly to remove the enzyme from the blood stream. In the presence of renal impairment pepsinogen excretion is impaired.

3. A second extragastric proteolytic enzyme system (cathepsin), also active at pH 1.5, is not excreted by the kidney and thus is biologically differentiated from pepsinogen.

4. A method is described of collecting gastric venous blood to measure alterations in gastric peptic activity as reflected by blood pepsinogen levels.

5. Blood pepsinogen levels in gastric venous blood are elevated following the administration of the peptic secretagogues Mecholyl and ACTH.

6. Histamine has an effect upon blood pepsinogen concentration only when administered in massive dosages.

7. Various operative preparations associated with experimental ulcerogenesis were not productive of significant alteration in blood pepsinogen levels.

8. The consistent depression of blood pepsinogen levels by vagotomy suggests the use of this determination in assessing the completeness of vagus division.

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EFFECTS OF VARIOUS ALTERATIONS OF PERITONEAL FLUID RESULTING FROM EXPERIMENTAL STRANGULATED INTESTINAL OBSTRUCTION

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AMONG the factors which contribute to death following intestinal obstruction are fluid and electrolyte loss, blood loss, and perforation with peritonitis. The mechanism of death of experimental animals following strangulation of a short segment of ileum has not been clearly established. These animals do not live long enough to develop fluid or electrolyte problems. Blood transfusions do not prevent a lethal outcome. Post-mortem examination reveals no evidence of suppurative peritonitis. Large amounts of dark fluid may be consistently recovered from the peritoneal cavities of animals dying of strangulated obstruction of a short segment. If an isolated, strangulated closed loop of ileum is placed in a plastic bag so that exposure of the animal to the fluid is prevented, life is indefinitely prolonged. Perforation of the bag with escape of its contents is followed by a rapid downhill course and death of the animal.[2] It was concluded that this material played a significant role in the ultimate fate of these animals. The following studies were concerned with the effects of various alterations and fractionations of this fluid.

MATERIALS AND METHODS

Nine large adult mongrel dogs served as donors for the peritoneal fluid used in these studies. Utilizing fractional intravenous Nembutal for anesthesia, a low midline abdominal incision was made. A 10 cm. segment of ileum was strangulated by dividing the veins in the mesentery and those vessels parallel to the longitudinal axis of the bowel. Ties of umbilical tape were used to encircle the bowel, effecting a closed loop obstruction.[1] At or shortly before death, the peritoneal cavity was opened for withdrawal of the accumulated peritoneal fluid. These animals were divided into 3 equal groups so that 3 aliquots of fluid were recovered.

Aerobic and anaerobic cultures of the fluid were made. Nine normal animals were given intraperitoneal injections of the unaltered fluid in the amounts of 4 c.c. per kilogram of body weight. Light anesthesia with intravenous Nembutal was induced before the injections were administered.

Five hundred cubic centimeters of unaltered fluid were autoclaved along with the surgical instruments. Five normal animals received an intraperitoneal injection of this material (4 c.c. per kilogram).

Five hundred cubic centimeters of unaltered fluid were centrifuged at 700 r.p.m. for 10 minutes. The sediment which was recovered by removing the

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supernatant fluid was thoroughly washed and resuspended to its original volume with isotonic saline. It was then injected into the peritoneal cavities of 5 normal dogs (4 c.c. per kilogram).

A portion of the supernatant fluid which resulted from centrifugation was injected into the peritoneal cavities of 4 normal dogs (4 c.c. per kilogram). Another portion of this fluid was placed in a heated water bath so that the temperature was maintained at 60° C. for 10 minutes. It was then injected into the peritoneal cavities of 6 normal dogs (4 c.c. per kilogram).

One hundred cubic centimeters of supernatant fluid was exposed to 125,000 units of crystalline trypsin for 10 hours. This mixture was incubated at 36° C. for 8 hours. It was injected into the peritoneal cavities of 2 normal animals (4 c.c. per kilogram).

Fractionation of the supernatant fluid resulting from centrifugation of 500 c.c. of unaltered fluid was carried out.[4]

Fraction I.—This material was precipitated between 0° and 3° C. by adding 8 to 10 per cent ethanol at pH 7.

Fractions II and III.—To recover this portion the ethanol concentration was raised to 25 per cent while the temperature was lowered to 5° C. The last fraction was obtained by lowering the pH to 5.2 and altering the ethanol concentration to 17 per cent.

Fraction IV.—This constituent was recovered by raising the ethanol concentration to 40 per cent and adjusting the pH to 5.8.

Each of these fractions was injected in equal portions into the peritoneal cavities of 2 normal dogs. After completion of the above fractionations, the remaining fluid was exposed to chemically pure chloroform. A gelatinous material which collected between the chloroform and alcohol layers was removed and injected into the peritoneal cavities of 3 normal animals.

The remaining alcohol fraction was given intravenously to one normal dog.

Normal dog blood was carried through the same process as described above, following which the precipitate found between the chloroform and alcohol layers was injected into the peritoneal cavity of a normal dog.

The second method of fractionation was begun by centrifugation of the raw fluid. The supernatant fluid (100 c.c.) was cooled to −1° C. Absolute alcohol (10 c.c.) was added, following which the precipitate was removed by centrifugation. This was resuspended in 10 c.c. of saline and labeled fraction one. By adding 10 c.c. of alcohol each time, this process was repeated until 10 fractions were obtained. Each fraction was injected directly into the peritoneal cavity of one dog. This procedure was repeated using a second 100 c.c. aliquot of fluid.

Observations for survival of animals in all groups were carried out for 48 hours.

RESULTS

Donor animals lived for 24 to 30 hours. Their postoperative course was normal until about 2 hours before death, when they rather suddenly developed

rapid respiratory rates, became lethargic, and then comatose. From 200 to 400 c.c. of dark, foul fluid was removed from the peritoneal cavity of each animal. Although there were no areas of gross perforation, the obstructed intestinal segments were collapsed. Culture of this fluid revealed *Proteus vulgaris,* beta hemolytic streptococcus, *Escherichia coli,* and *Clostridium welchii.*

The lethal properties of the raw fluid were demonstrated by injection of this material into the peritoneal cavities of 9 normal animals. All were dead within 7½ hours (Table I).

TABLE I. RESULTS OF INTRAPERITONEAL INJECTION OF UNALTERED FLUID

DOG NUMBER	WEIGHT (KG.)	DOSE (4 C.C./KG.)	LENGTH OF LIFE (HOURS)	DONOR ANIMALS (GROUP)
132	9	36	4.50	I
121	8	32	4.25	I
199	6	24	4.00	I
119	10	40	5.00	II
139	9	36	4.30	II
158	9	36	4.25	II
128	8	32	6.00	III
5	9	36	7.30	III
68	7	28	5.25	III

The autoclaved fluid produced no deletrious effect of lethal proportions when placed into the peritoneal cavities of normal animals. All 5 dogs recovered completely following this procedure.

The 6 animals who received the fluid which was held at 60° C. for 10 minutes all recovered. Those 2 who received the trypsin-treated fluid were dead within 8 hours.

Intraperitoneal injection of the resuspended sediment which was recovered following centrifugation of raw fluid was not fatal. All animals recovered completely. This was in marked contrast to those animals who received the supernatant fluid. They were all dead within 7 hours (Table II).

TABLE II. LETHAL PROPERTIES OF ALTERED FLUID

NUMBER OF DOGS	MODIFICATION OF FLUID	DOSE (C.C./KG.)	SURVIVORS
5	Autoclaved	4	5
4	Centrifuged supernatant fluid	4	0
5	Sediment	4	5
6	Temperature elevated to 60° C. for 10 minutes	4	6
2	Exposed to trypsin	4	0

Following intraperitoneal injection, none of the 5 protein fractions recovered by the first method produced a lethal result. All 3 of the animals who received the chloroform fraction died. Intravenous administration of the remaining fraction was followed by complete recovery of the animal (Table III). The chloroform fraction which resulted from processing normal dog blood was not lethal following injection into the peritoneal cavity of a normal animal.

TABLE III. RESULTS FOLLOWING INJECTION OF VARIOUS FRACTIONS OF 500 C.C. OF RAW FLUID

NUMBER OF DOGS	FRACTION	SURVIVORS
2	I	2
2	II and III	2
2	IV-1	2
2	IV-4	2
3	Chloroform-alcohol	0
1	Remaining	1

The second method of fractionation was carried out twice. When injected into the peritoneal cavities of normal dogs, those of the first group who received fractions 2, 3, and 4 died. The remaining 7 animals recovered. Those animals of group 2 who received fractions 1, 2, 3, and 4 died. The remaining 6 animals recovered (Table IV).

TABLE IV. RESULTS OF FRACTIONATION OF FLUID (200 C.C.) BY ALTERING THE ALCOHOL CONCENTRATION

FRACTION	NUMBER OF DOGS INJECTED	SURVIVORS
I	2	1
II	2	1
III	2	0
IV	2	0
V	2	1
VI	2	2
VII	2	2
VIII	2	2
IX	2	2
X	2	2

DISCUSSION

That the fluid which accumulates in the peritoneal cavities of dogs dying of strangulated intestinal obstruction is lethal when placed in the peritoneal cavities of normal animals is now well established. One animal will produce enough toxic fluid to kill 7 animals of equal size. This material has been shown to contain many bacteria, but there is considerable evidence to indicate that bacteremia alone is not the cause of death. The pink fluid seen to accumulate in the peritoneal cavity early in the course of strangulated obstruction is not lethal, yet it contains the same bacteria as found in the late toxic fluid.[3] At autopsy the peritoneal cavity did not present the findings characteristic of a late bacterial peritonitis. Cultures of pure *Clostridium welchii* were not fatal in the absence of necrotic tissue.[3] The toxic effect of the fluid was destroyed by autoclaving. Further evidence that the toxin was heat labile was gained when the material was rendered nontoxic by maintaining the temperature at 60° C. for 10 minutes. These findings are compatible with those to be expected if the toxin were a protein. Of the fractions obtained by the method where chloroform was used, only one was found to be toxic. When normal dog blood was subjected to the same process, a similar-appearing material was recovered, but it did not kill the animal when injected into the peritoneal cavity.

Utilizing the second method, it was possible to precipitate the toxin along with other elements of the protein content. Further investigative work aimed at purification and refinement of this fraction is in progress.

CONCLUSIONS

1. Large amounts of lethel fluid were recovered from the peritoneal cavities of animals dying of strangulated intestinal obstruction.

2. The bacterial content of this material included *Proteus vulgaris,* beta hemolytic streptococcus, *Escherichia coli,* and *Clostridium welchii.*

3. The lethal properties of the fluid were eliminated by heat.

4. The sediment recovered by centrifugation of raw fluid was not lethal in contrast to the supernatant portion.

5. It was possible to localize the toxin to various portions following fractionations of the supernatant fluid.

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RECONSTRUCTION OF THE ESOPHAGUS WITH WIRE MESH PROSTHESIS

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ALTHOUGH numerous attempts have been and are being made to develop a means of re-establishing esophageal continuity following esophageal resection, none to date have solved the problem with complete satisfaction. The Wookey operation for reconstruction of the cervical esophagus, the utilization of skin grafts over wire gauze,[5] esophagogastrostomy, extrathoracic esophagoplasty, skin tubes, colonic esophagoplasty, intrathoracic esophagojejunostomy, and plastic tube reconstruction[2] all have been of value in advancing esophageal surgery and all have been successfully applied. Each procedure, however, has certain disadvantages which have prevented it from becoming universally adopted. Anastomotic leakage, postoperative stricture, infection, prolonged morbidity, complexity of the surgical technique, and limitation of blood supply when using intestinal transplants continue to be troublesome complications.

Plastic tube reconstruction of the esophagus as first used by Berman,[2, 3] one of the newer methods, has technical simplicity as one of its major advantages. It has been felt, however, that there were certain disadvantages in the use of a synthetic esophageal prosthesis which required improvement. There is a tendency for leakage to occur with subsequent infection around the anastomosis at the junction of the rigid graft and the esophagus. Most of the sutures holding the plastic tubes in place will eventually cut through and the prosthesis is passed or removed deliberately by the surgeon. A tissue tube with an external fibrous layer and an internal layer of epithelium remains, but over an extended period of time this area often undergoes stricture formation. This study was carried out in an attempt to provide a method which would overcome these drawbacks.

METHOD AND MATERIALS

It was felt that placement of a wire mesh external to the synthetic tube would provide a permanent frame for the mucosa and fibrous tissue, and the rigidity of the wire would prevent stricture formation. Although stainless steel wire is a relatively nonreactive material, it is rapidly encased in fibrous tissue and, within a short time after its insertion, the anastomotic areas are sealed off. Any tendency toward leakage is thus considerably decreased.

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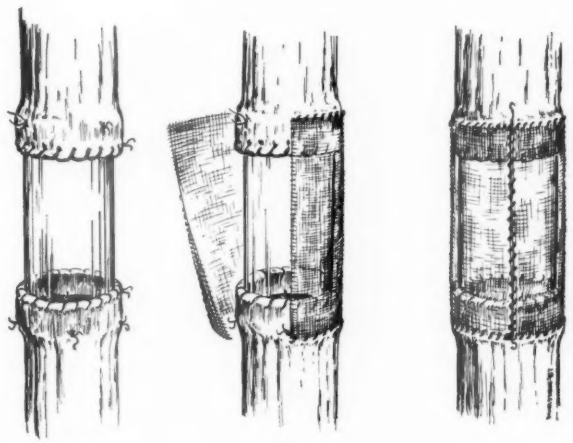
Flexible Tygon tubing could easily be sutured and because of the nature of this synthetic material, it tended to seal itself about the suture hole, thus decreasing leakage. Tubing 18 mm. in outer diameter and 2 mm. in thickness was cut to the desired length. The ends of the tube were beveled with a scalpel to about 1.5 mm. thickness in order to facilitate the insertion of the sutures and insure a snug fit to the esophageal mucosa. Fifty by fifty Surgaloy* steel mesh made of stainless steel wire U.S.P. 0.003 inch in diameter was obtained in sheets and cut to size at the time of the operation.

EXPERIMENTAL DATA

Sixteen mongrel dogs weighing from 18 to 30 pounds were used. Each animal was placed on a 24-hour bowel preparation of Sulfasuxidine, and food and water were withheld for 12 hours preoperatively. Intravenous Nembutal anesthesia was employed. Oxygen was administered by a positive pressure respirator through an endotracheal tube.



A. *B.* *C.*

Fig. 1.—Tygon tube sutured in place in esophagus with inner row of interrupted silk tacking sutures and outer row of continuous chromic catgut (*A*). Wire mesh extending beyond cut edge of esophagus sutured around cut edge of esophagus (*B* and *C*).

A standard right lateral thoracotomy incision was performed through the fourth intercostal space. The azygos vein was divided and the mediastinal pleura dissected from the esophagus with care. The esophagus was freed for several inches and the lower end tied with umbilical tape to prevent regurgitation of gastric contents.

The mid-esophagus was divided after placing stay sutures through the muscularis for traction. A 5 to 6 cm. segment of mid-esophagus was resected. Four interrupted 3-0 silk sutures were placed at each end of the Tygon tube, which was approximately 8 cm. in length. These tacking sutures were placed through the esophageal wall one half inch from the cut proximal end and tied in place. A continuous running stitch of 3-0 chromic catgut was used to attach the cut edge of the esophagus to the Tygon tubing. The Tygon tube was then fastened to the distally divided esophagus in identical fashion.

*Manufactured by Davis & Geck, Inc., Danbury, Conn.

A rectangular piece of Surgaloy mesh the same length as the Tygon tubing was cut to size and placed around the tubing. It thus reached to the layer of the interrupted sutures 0.5 cm. beyond the cut edge of the esophagus. It was sutured in place with 3-0 chromic catgut after rolling its edges to prevent fraying. (Fig. 1.) The esophagus was replaced in the mediastinum and the pleura closed over the prosthesis.

Penicillin and streptomycin were instilled into the chest which was closed in layers. Antibiotics were used for 10 days postoperatively. Earlier in the series, the dogs were maintained on nothing by mouth with intravenous feedings for 10 to 14 days following operation. It was soon found possible to reduce this period to a week without any untoward results. They were then started on liquid diet for 24 to 48 hours, advanced to a soft diet, and by the end of the second week were able to take regular diet well.

RESULTS

Of the 16 dogs in the series none died of anastomotic leakage. The first dog in the series did well for 2 weeks and, when first given liquids by mouth, aspirated a large amount of milk. At autopsy 3 weeks postoperatively, extensive bronchopneumonia was evident. No infection was present in the mediastinum or pleural cavity. There was a good fibrous reaction about the Surgaloy mesh, completely sealing it and preventing any possible leakage. Islands of epithelium were seen covering the inner aspect of the wire mesh extending down from the cut esophageal edge which was firmly plastered to the wire screening. The Tygon tube remained in place.

One dog died of distemper 2 months postoperatively. There were no complications relative to the esophageal prosthesis, both clinically and at post-mortem examination.

TABLE I

DOG NUMBER	POSTOPERATIVE INTERVAL AT FOLLOW-UP	FINDINGS AT FOLLOW-UP EXAMINATION
106-56	3 weeks	Died, bronchopneumonia, patent esophagus, early epithelialization, no leakage
26-56	3 months	Sacrificed, partial compression wire mesh
146-56	2 months	Died, distemper, good esophageal lumen
153-56	4 months	Sacrificed, moderate compression wire mesh, narrowed patent lumen
125-56	3 months	Sacrificed, wire mesh compressed by trachea, lumen narrow
104-56	3 months	Sacrificed, wire mesh compressed by trachea, lumen narrow
145-56	3 months	Sacrificed, good patent esophageal lumen, well epithelized
38-56	4 months	Sacrificed, good esophageal filling on x-ray, patent esophageal lumen
113-56	5 months	Alive and well, good esophageal lumen on x-ray
147-56	4 months	Alive and well, good esophageal lumen on x-ray
150-56	4 months	Alive and well, good esophageal lumen on x-ray
151-56	4 months	Alive and well, good esophageal lumen on x-ray
154-56	4 months	Alive and well, good esophageal lumen on x-ray
49-55	4 months	Alive and well, good esophageal lumen on x-ray
69-54	4 months	Alive and well, good esophageal lumen on x-ray
114-56	5 months	Alive and well, good esophageal lumen on x-ray

None of the remaining 15 dogs died of postoperative complications (Table I). Clinically there was no evidence of infection or anastomotic leakage. Thoracentesis in the immediate postoperative period in several instances revealed only serosanguineous fluid.

Barium esophagrams were taken between 2 and 4 months postoperatively. In 4 of the dogs some compression and kinking of the wire was seen on fluoroscopy. These dogs were sacrificed 2 to 4 months postoperatively, at which time their state of nutrition was poor. It was found that in these animals, the Tygon tube had already passed, and the esophagus which had been replaced in its original position between the trachea and vertebral column in order to repleuralize was flattened behind the trachea. In each instance, it was at the tracheal bifurcation that the stiff trachea compressed the very flexible Surgaloy mesh and kinked it, and it was at this point that the esophageal lumen was markedly narrowed. Several dogs that showed a good state of nutrition and good filling in the area of the esophageal prosthesis on x-ray were sacrificed 2 to 4 months postoperatively. At autopsy there was also a good fibrous tissue reaction about the outside of the wire screen and a shiny smooth coating of epithelium on the inside (Fig. 2). In these dogs, the Tygon tube had passed. In the group in which stricture and compression were not a problem, it was found that the esophagus, although placed in the mediastinum, had not been replaced beneath the trachea.

Fig. 2.—Specimen taken from Dog No. 145-56 sacrificed 3 months postoperatively showing shiny smooth epithelium on inside of wire mesh.

The rest of the dogs are alive, are in a good state of nutrition 4 months postoperatively, and demonstrate good esophageal filling radiographically (Fig. 3).

Sections taken from the tissue on the inner surface of the wire mesh showed stratified squamous epithelium resting upon a layer of longitudinally

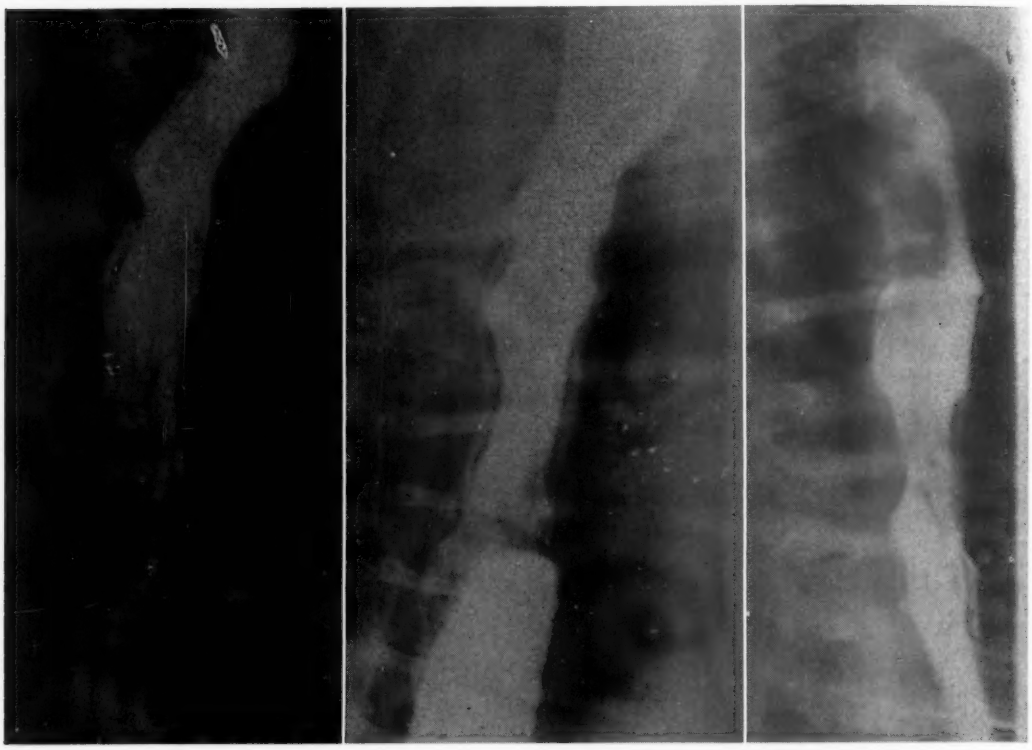


Fig. 3.—Barium esophagrams taken 3 to 4 months postoperatively showing good filling in region of wire prosthesis. Dog No. 69-54 (*A*), Dog No. 114-56 (*B*), Dog No. 150-56 (*C*).

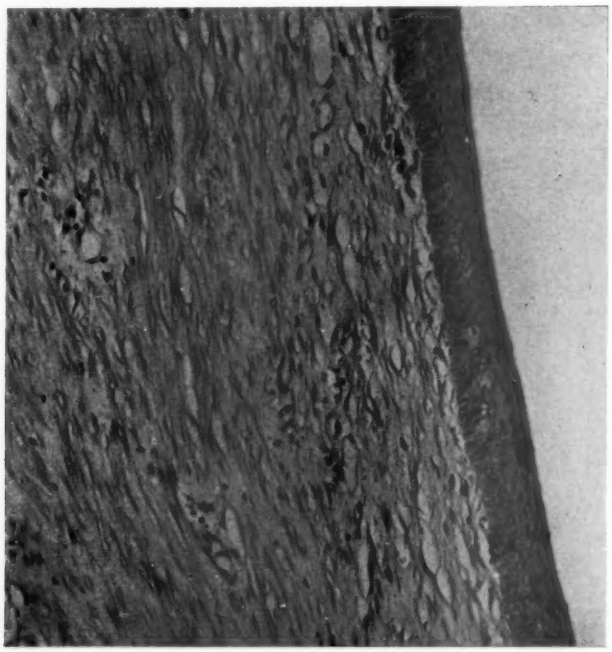


Fig. 4.—Photomicrophotograph (×124) of section from tissue on inner surface of wire mesh 3 months following surgery.

arranged smooth muscle cells. On the mediastinal surface of the wire mesh, fibrous tissue encased the prosthesis. (Fig. 4.)

DISCUSSION

The use of a strut of wire mesh around a plastic tube to bridge the gap following esophageal resection has been demonstrated to have certain advantages. Because of its tendency to induce an early fibrous tissue reaction on the part of the host, the suture line is soon sealed off and anastomotic leakage is almost eliminated if the plastic tube is sutured in place in such a way as to be watertight for the first few days. This can be attained with the flexible Tygon tubing. Repleuralization about the prosthesis provided a tissue layer which can rapidly adhere to the wire and aid in the sealing process. The tendency for infection to develop around wire is significantly less than around such materials as Ivalon, nylon, or other fabrics. The fibrous tissue grows into the interstices of the wire mesh and holds it solidly in position to remain as a permanent support for the newly formed esophageal tube.

The wire mesh used in this series was woven of very fine strands and had extreme flexibility. It is felt that the utilization of a stiffer mesh will reduce the incidence of postoperative esophageal narrowing due to kinking and secondary stricture since the heavier wire will be much more able to retain its molded form against extraluminal pressures. A pleural flap can then be dissected from the lateral thoracic wall to aid in forming a protective seal about the prosthesis.

SUMMARY

1. A method of esophageal reconstruction is presented which consists of the placement of a wire screen around a Tygon tube.

2. This procedure was applied in 16 dogs and found to be technically simple.

3. This method shows promise of decreasing the incidence of stricture and postoperative anastomotic leakage.

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THE EFFECT OF SYMPATHECTOMY AND ADRENALECTOMY ON GASTRIC INHIBITORY PROPERTY OF INSULIN

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INSULIN-induced hypoglycemia stimulates secretion and motility of the stomach; this is a central nervous phenomenon and is transmitted by the vagus nerves. Since this effect is abolished by vagotomy, it has been used as a test of presence or absence of vagus innervation to the stomach both in experimental animals and in man. After intravenous administration of insulin, there is a delay of 25 to 40 minutes before hypoglycemic symptoms and stimulation of the stomach occur. During this intervening period, a depression of both secretion of gastric juice and motility is usually observed. Burstall and Scholfield[1, 2] used dogs prepared with denervated gastric (Heidenhain) pouches and found that gastric secretion stimulated with a cholinergic drug (urethan of β-methylcholine chloride) could be inhibited by insulin hypoglycemia. Karvinen and Karvonen[13] found that histamine-induced secretion from Heidenhain pouches was similarly inhibited by insulin. This inhibition depends upon the production of hypoglycemia, since insulin given with glucose has no depressant effect. Hypoglycemia produces sympathetic as well as parasympathetic stimulation. Forrest and Code[10] have demonstrated, however, that celiac ganglionectomy has no effect on the inhibitory effect of insulin. It is known that epinephrine inhibits gastric secretion.[11] It has been shown that hypoglycemia causes release of adrenalin[3, 5, 6, 9, 12] and that the urinary excretion of adrenalin falls about 80 per cent after bilateral adrenalectomy.[7, 8] Stimulation of the adrenal medulla might in this way result in inhibition of gastric secretion. Noradrenalin, the neurohormone of the sympathetic nerves, is released into the blood and excreted in the urine; this substance might also intermediate the inhibitory effect of insulin hypoglycemia on the stomach. Therefore, it is the purpose of the present study to determine the effect of insulin hypoglycemia in animals with bilateral adrenalectomy, total thoracolumbar sympathectomy, and both.

METHOD

Adult mongrel dogs weighing 16 to 20 Kg. were first prepared with Heidenhain pouches. Gastric secretion was stimulated by small, regular doses of

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histamine as described by Code and associates.[4] After a plateau secretion was obtained, the animal was given insulin intravenously, while the histamine stimulation was continued as before.

Total sympathectomy was then performed as a multistage procedure. Usually 4 stages were used, 2 transthoracic and 2 translumbar. The thoracic approach was made through the sixth intercostal space, and, by using lighted retractors and head lamps, it was possible to remove the ganglionated chain from the stellate ganglion to the last thoracic ganglion at the posterior reflection of the diaphragm. The lumbar ganglia were exposed transperitoneally through a long diagonal incision extending inferomedially from the costovertebral angle. In dogs in which adrenalectomy was also to be used, this procedure was usually performed along with ipsilateral lumbar sympathectomy. A recovery period of 2 to 3 weeks was allowed between stages.

Animals which had bilateral adrenalectomy were maintained on intramuscular cortisone of 12.5 to 25 mg. daily. After complete recovery from surgery and stabilization of the replacement therapy, intravenous insulin was again given during the course of a continuous histamine test. Adequacy of hypoglycemia was confirmed by blood glucose determination in all experiments; a fall to 50 per cent or less of the fasting level was considered sufficient.

RESULTS

Studies on 4 dogs form the basis of this report.

Dog No. 1 had total thoracolumbar sympathectomy. On 2 occasions continuous histamine response was clearly inhibited; an example of this is presented in Table I.

TABLE I. INHIBITION OF GASTRIC SECRETION BY INSULIN IN DOG WITH TOTAL SYMPATHECTOMY

Histamine phosphate 0.1 mg. subcutaneously every 10 minutes; gastric juice collections from Heidenhain pouch

TIME (HOURS)	VOLUME (C.C.)	FREE ACID CLINICAL UNITS	HCl OUTPUT (mEq.)
1,030-1,100	2	70	0.14
1,130	2	75	0.15
1,200	2.5	115	0.29
1,230	2.5	120	0.30
8 units insulin intravenously			
1,300	2	120	0.24
1,330	0	0	0.00
1,400	0	0	0.00
1,450	2	80	0.16

Dog No. 2 had bilateral adrenalectomy. Insulin administered intravenously during continuous histamine stimulation strongly inhibited the secretion of acid gastric juice from the Heidenhain pouch.

Dogs Nos. 3 and 4 had total thoracocolumbar sympathectomy plus bilateral adrenalectomy. Three tests were performed in one animal and 2 in the other. A definite inhibitory effect followed insulin administration in all 5 experiments. An example is presented in Table II.

TABLE II. INHIBITION OF GASTRIC SECRETION BY INSULIN AFTER TOTAL SYMPATHECTOMY AND BILATERAL ADRENALECTOMY

Histamine phosphate 0.025 mg. subcutaneously every 10 minutes; collections from Heidenhain pouch

TIME (HOURS)	VOLUME (C.C.)	FREE ACID CLINICAL UNITS	HCl OUTPUT (mEq.)
1,030-1,100	6	125	0.75
1,130	6	130	0.78
1,200	6	130	0.78
6 units insulin intravenously			
1,230	2.5	110	0.28
1,300	1.5	80	0.12
1,330	0.5	0	0.00
1,400	3.5	80	0.28
1,430	2.5	90	0.23

DISCUSSION

The results presented indicate that the initial inhibitory effect of intravenously administered insulin on the secretion of acid gastric juice is probably not the result of noradrenalin liberated from sympathetic ganglia or epinephrine secreted by the adrenal medulla. The possibility remains that epinephrine and like substances were released from other tissues. Autopsy in all animals, however, failed to reveal any residual sympathetic ganglia. Similarly, in none of the 3 adrenalectomized animals was there residual adrenal tissue present. A drastic reduction in the presence of these substances is inferred from the work of others, and determination of blood and urine levels of adrenlin and noradrenalin was not done. Since a small amount of adrenalin is still excreted in the urine after complete adrenalectomy, inhibition of gastric secretion might still occur. Powerful suppression by the insulin of relatively high gastric secretory levels makes this seem unlikely.

Thus, the mechanism by which insulin hypoglycemia inhibits gastric secretion prior to the onset of vagal stimulation has not been revealed by the present study. It has been hypothesized that this inhibition is a nonspecific effect resulting from the diminished amount of carbohydrate substrate available to the parietal cell.[4] Evidence to support this theory awaits further work.

SUMMARY AND CONCLUSION

Insulin-induced hypoglycemia has a biphasic effect on gastric secretion, with a period of inhibition followed by excitation. Although the stimulation is transmitted by the vagus nerves, no explanation has been forthcoming for the inhibitory phase. Adrenalin and noradrenalin are released by insulin hypoglycemia and are known to inhibit gastric secretion. Dogs were prepared with total thoracolumbar sympathectomy, bilateral adrenalectomy, and both. However, insulin-induced hypoglycemia powerfully inhibited the secretion of acid gastric juice in all 4 dogs studied. It is concluded that the inhibitory effect of insulin on gastric secretion probably does not result from release of adrenalin or noradrenalin.

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PAPILLARY CARCINOMA OF THE THYROID
An Evaluation of Surgical Therapy

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TUMORS with papillary components are the most frequent malignant tumors of the thyroid gland. These tumors are peculiar biologically because the bearer usually remains in good health and lives a relatively long time even though regional lymph nodes may be invaded early and the patient harbors living tumor cells either in the thyroid gland, lymph nodes, lungs, or bone. The development of a rational plan of therapy is especially difficult because of the discrepancy between the rapidity of biologic progression as evidenced by early metastasis and the slowness of the clinical course of the disease. Consequently, contradictory ideas[9] are bound to arise regarding the best treatment of papillary carcinoma of the thyroid. Routine radical neck dissection is recommended by Frazell and Foote[5, 6] while Crile[1] looks upon complete removal of the primary as the important surgical procedure. He does not recommend that the conventional radical neck dissection accompany this, relying upon his observation that the greatest hazard to the patient with a papillary thyroid cancer lies in uncontrolled disease in the central zone of the neck. Frantz,[4] and MacDonald,[8] and others have demonstrated that multiple foci of origin occur in papillary thyroid cancer and that the contralateral lobe will be the site of an unsuspected primary focus in some cases. Thus contralateral metastases also constitutes a therapeutic problem. In the management of cancer in general, cosmetic factors should not be a consideration in planning surgical treatment. However, in the case of the tumor under discussion, the frequency in young women as well as the prolonged course has allowed cosmetic aspects to influence the plan of therapy recommended by some authors. In a previous communication one of us (C. E.) and L. T. Byars[3] described an operation in which the sternocleidomastoid muscle was preserved if no gross evidence of invasion was found and the submaxillary triangle was not routinely dissected. When combined with an incision which follows natural skin folds, block dissection can be carried out without significant deformity. During the interval from 1929 to 1955 this operation along with a variety of others has been utilized in treating this tumor in 62 patients at the Barnes Hospital. In some

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cases in this series a sufficient period of time has elapsed to permit an evaluation of the results of treatments considered by most surgeons today to be inadequate. Since it is only by the correlation of pathologic findings, treatment, and end results that differences of opinion will be resolved, we have reviewed the clinical data, operations, pathologic findings, and follow-ups on this series of 62 patients. The study thus conducted forms the basis for this report.

AGE AND SEX DISTRIBUTION

The proportion of women to men is over 4 to 1, a sex distribution similar to that found by others. Of the 5 patients below the age of 20 years with this tumor, all were women. In this series papillary thyroid cancer was seen later in life in men than in women (Table I).

TABLE I. DISTRIBUTION OF PATIENTS ACCORDING TO AGE AND SEX

AGE IN YEARS	FEMALE	MALE
0-10	3	
10-20	2	
20-30	13	1
30-40	9	2
40-50	12	1
50-60	4	2
60-70	7	6

SYMPTOMS AND SIGNS

The most common presenting symptom was that of a single nodule within the thyroid (53 per cent). In 8 patients lymph node enlargement in the cervical lymph node chain was the presenting finding, and in none of these cases was a thyroid tumor palpable. In 16 patients a tumor in the thyroid was seen in association with lymph node enlargement. Thus 24 patients (39 per cent) had lymph node enlargement as a major presenting finding when first seen (Table II).

TABLE II. PRESENTING SIGNS AND SYMPTOMS IN REGARD TO LYMPH NODE ENLARGEMENT

SYMPTOMS	NUMBER	PER CENT
1. Involvement of thyroid only	38	61
2. Involvement of lymph nodes only	8	13
3. Involvement of thyroid and lymph nodes	16	26
Total	62	100

Although the presumptive diagnosis of thyrotoxicosis was made rather often, with but few exceptions, it was made on the basis of clinical evidence only and was not corroborated by the finding of a high basal metabolic rate, high protein-bound iodine levels, or rapid I^{131} uptakes.

In several cases a cystic tumor beneath the sternocleidomastoid muscle led to the preoperative diagnosis of branchial cleft cyst.

When the presenting findings consist of a mass in the thyroid with enlarged lymph nodes in the deep cervical chain, particularly in younger individuals, a preoperative presumptive diagnosis can be made with some accuracy. However, the exact diagnosis cannot be made until pathologic examination is

carried out. In this connection some word is necessary about the use f frozen sections in the immediate diagnosis of these lesions. Most authors mention this only to dismiss it as of little value because of its inaccuracy. On the contrary we have found it to be useful on numerous occasions. In a recent review of a group of 63 frozen sections performed upon various lesions of the thyroid at this hospital, no false positives were reported and only 2 false negatives, one of these being a papillary carcinoma.

There has been wide divergence of opinion in regard to the association of thyroid nodules and carcinoma. The pathologic study by Mortenson and co-workers[11] probably reflects most accurately the statistical probabilities. A detailed examination on the thyroid gland removed at 1,000 consecutive necropsies was carried out with the following findings: "A solitary nodule was present in 119 thyroid glands, which represented 12 per cent of all glands examined and 23 per cent of the nodular glands. A solitary nodule which was palpable to the examiner at necropsy with the gland actually in his hand, however, was found in only 26 thyroid glands . . . a solitary nodule, regardless of its palpability, is malignant in about 9 per cent of the cases. . . . The incidence of primary malignant neoplasia of the thyroid, therefore, was 2.8 per cent in the 1,000 consecutive routine necropsies, or 5.3 per cent in the 525 nodular thyroid glands."

There have been many reports concerning the incidence with which carcinoma occurs in the nodular gland and in particular in the gland containing a single nodule. It is not our purpose here to enter into a discussion of this problem but only to point out that in all these reports some definite correlation has been found.

It was of interest that of the 51 female patients in this group, 5 (9.8 per cent) had noted a close association of pregnancy with the appearance or progression of the tumor. Four of these 5 patients were found at the time of primary operation to have lymph node metastases and the other to have a lesion thought to have been incompletely removed. This rather striking association of papillary carcinoma of the thyroid with a known period of hormonal activity in the female further substantiates the previously known tendency of the tumor to alter its growth pattern in response to changes in the levels of hormonal balance. There have been reports of significant regression in growth of the tumor with the administration of testosterone and of thyroid hormone.[1] From a study of our cases, it would appear that when one encounters papillary carcinoma of the thyroid in the pregnant woman, the neoplasm is usually very active and locally far advanced.

PATHOLOGY

It has been pointed out previously that the diagnosis of papillary carcinoma of the thyroid is made in the great majority of instances by examination of the microscopic section of the tumor. One may, however, often suspect the lesion by close inspection of the cut surface of the tumor with a hand lens

for the presence of papillary formations. In those cases in which the metastasis is grossly cystic, this technique will likely be rewarding, for the finding of a cystic structure within the neck containing a hemorrhagic fluid and possessing a roughened lining should arouse suspicion of the presence of papillary thyroid carcinoma (Fig. 1).

We have chosen to separate this group of cases into those which, on microscopic section, demonstrated a pure or predominantly papillary pattern and those which contained a mixture of both papillary and follicular elements. Our findings in regard to the pathologic examination of the specimen are summarized in Table III. The group of pure or predominantly papillary tumors comprised 64 per cent of our cases, while the group of mixed papillary and

Fig. 1.—Photomicrograph demonstrates papillary formation within a cyst in the neck. This cyst contained fluid and along its wall was a slightly elevated zone. Microscopic section showed this to be a papillary cancer within a lymph node which had undergone cystic degeneration.

TABLE III. INCIDENCE OF CELL TYPE AND OF LYMPH NODE METASTASES

	NUMBER	PER CENT
1. Pure or predominantly papillary carcinoma		
a. No lymph nodes included with specimen	21	34
b. Lymph nodes free of metastases	2	3
c. Lymph nodes with metastases	17	27
2. Mixed papillary and follicular carcinoma		
a. No lymph node included with specimen	12	19
b. Lymph nodes free of metastases	1	2
c. Lymph nodes with metastases	9	15
Total	62	100

follicular tumors comprised 36 per cent. It is our present feeling that all primary neoplasms of the thyroid with papillary components should be classified as papillary carcinoma regardless of the proportionate distribution of papillary and follicular elements.

The presence of psammoma bodies (Fig. 2) in a papillary lesion of the thyroid is, in our opinion, an indication that the lesion is malignant. When seen on frozen section this finding is also of assistance to the pathologist in enabling him to arrive at the correct diagnosis. In instances in which they are concentrated in large aggregates, they may be visible radiographically in both the thyroid and involved regional lymph nodes.

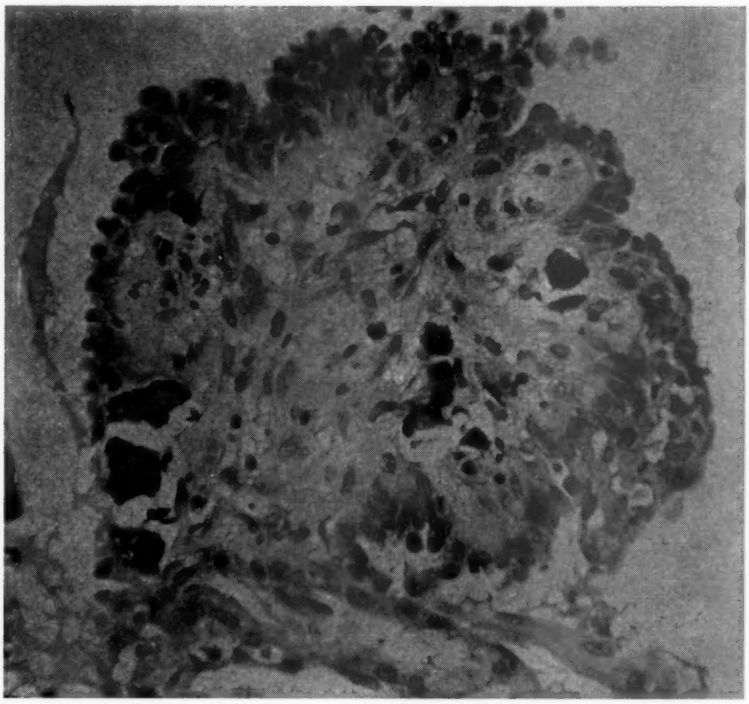

Fig. 2.—Photomicrograph demonstrates well-formed psammoma bodies within a well-differentiated frond of a papillary cancer.

The question of the frequency with which this neoplasm metastasized to the regional lymph nodes of the neck is obviously important in determining the need for surgical removal of the lymph nodes. We found that the tumors classified as pure or predominantly papillary on microscopic section metastasized to the cervical lymph nodes in 27 per cent of the total cases. In the group of mixed papillary and follicular tumors, such metastases were encountered in 15 per cent of the total cases, making an over-all incidence of 42 per cent. This figure takes into account all specimens submitted for examination which, of course, include several local excisions in which no lymph nodes were obtained. If one considers only those specimens in which the pathologist obtained lymph nodes, the incidence of proved metastases rises to 90 per cent.

This includes many specimens in which the only lymph nodes submitted were those lying adjacent to the gland and obtained incidentally at the time of lobectomy. Had more extensive resection been done, this alarmingly high incidence of lymph node metastasis might well have been even higher.

Another interesting pathologic feature of this tumor also of significance in considering the correct surgical approach is the occurrence of multiple primary foci of origin involving not only the same lobe but also the isthmus and contralateral lobe (Fig. 3). In Table IV it will be noted that when both lobes were

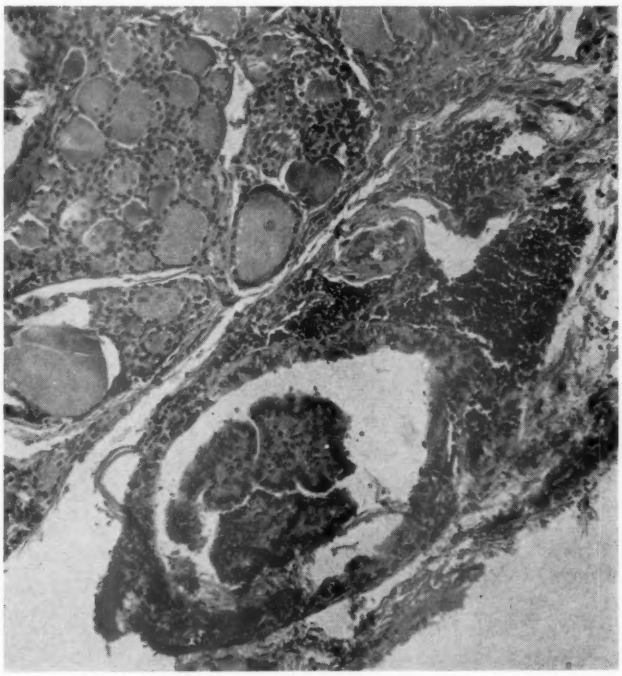

Fig. 3.—Photomicrograph demonstrates a small focus of papillary cancer within the apparently uninvolved opposite lobe.

TABLE IV. CASES IN WHICH BOTH LOBES OF THE THYROID GLAND WERE REMOVED

	NUMBER	PER CENT
1. Opposite lobe free of tumor	17	68
2. Opposite lobe containing multicentric focus or foci	8	32
Total	25	100

submitted for pathologic examination we encountered a second focus of tumor in the contralateral lobe in 8 (32 per cent) of 25 determinate cases. We believe the origin of these small foci to be questionable, for they may represent foci of lymphatic dissemination within the gland as well as true multiple foci of origin. Tumor has been found in the capsule and at times within what appear to be definite lymphatic channels. It is suspected that involvement of the opposite lobe would be found with much greater frequency if serial sections were performed.

OPERATIVE TREATMENT AND RESULTS

Sixteen different types of operations were performed in these 62 patients which reflects the diversity of surgeons as well as of concepts of "adequate therapy." In 48 patients the operation was the first to be carried out, while in 14 previous surgery had been performed at other institutions. This usually consisted of the removal of a lymph node from the neck or of a nodule from the thyroid. In either case the diagnosis had been established prior to treatment in this hospital. Reference to Table V will show that a total of 94 operations was carried out on these 62 patients. In the more recent period, 1950 to 1955, there is a trend toward a more radical approach, but in general neck dissection has only been carried out in the presence of clinical evidence of metastasis to lymph nodes.

The variation in clinical situations has contributed to the diversity of operations used. For example, one patient in this group was seen 10 days

TABLE V

OPERATIONS PERFORMED	1929-1944		1945-1949		1950-1955	
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
1. Local excision or enucleation of nodule of thyroid	1	8	5	20	4	7
2. Subtotal lobectomy	2	15	2	8	9	16
3. Bilateral subtotal lobectomy	2	15	3	12	3	5
4. Subtotal lobectomy with removal of lymph nodes	2	15	—	—	1	2
5. Subtotal lobectomy with radical neck dissection	—	—	—	—	1	2
6. Bilateral subtotal lobectomy with removal of lymph nodes	—	—	1	4	—	—
7. Total lobectomy	—	—	3	12	12	21
8. Total lobectomy with removal of lymph nodes	1	8	—	—	1	2
9. Total lobectomy with radical neck dissection	—	—	1	4	4	7
10. Total thyroidectomy	—	—	—	—	1	2
11. Total thyroidectomy with removal of lymph nodes	—	—	2	8	2	4
12. Total thyroidectomy with radical neck dissection	—	—	—	—	2	4
13. Biopsy of thyroid gland	—	—	3	12	—	—
14. Local excision of nodule or lymph node of neck	5	39	3	12	11	20
15. Radical neck dissection	—	—	1	4	3	5
16. Total lobectomy with contralateral subtotal lobectomy	—	—	1	4	2	3
Total	13	100	25	100	56	100

following the excision of a nodule in the isthmus of the thyroid. The sections showed not only a papillary carcinoma but evidence of inadequate local removal as well. No lymph nodes were palpable in either lateral neck region. It is quite apparent that in addition to considering further treatment of the primary lesion and regional lymph node metastases potential implantation into the previous operative wound also existed. Consequently, the second operation consisted of excision of the scar, total thyroidectomy, and removal of the ribbon muscles and all soft tissue between both carotid sheaths except the recurrent laryngeal nerves, one parathyroid gland, the trachea, and esophagus. During the second operation no lymph nodes over 5 mm. in size were seen; yet these nodes in both recurrent laryngeal chains contained cancer. Similar bilateral lymph node metastases have been observed in this series as well as by others[8] even when the primary tumor is evidently located in one lobe.

The follow-up in most cases consisted of a tumor clinic visit, personal examination by the individual surgeon, letter from the family physician following the patient, and, in a few instances, a letter from the patient. In 30 patients the examination included an x-ray of the chest. Five patients were lost to follow-up and 3 died of unknown causes at intervals following treatment. In these cases the status of the thyroid cancer could not be determined. Of the 8 cases with accurate follow-up treated between 1929 and 1944, one died of respiratory obstruction soon after a palliative operation. Six are alive and free of clinically detectable tumor. In this group is the patient in whom 2 lymph nodes in the deep cervical chain were locally removed without removal of thyroid tissue. Although of doubtful significance, it is of interest that in this group only local excisional operations were performed. Thus 6 (60 per cent) of the patients treated 17 to 28 years ago are known to be free of clinical evidence of disease at present. In the group treated 8 to 12 years ago, 3 have persistent cancer in the neck, one died of cancer, and only 7 of 14 are known to be free of disease. In the last group an insufficient period has elapsed for evaluation; however, one patient has already died of cancer and one patient

TABLE VI

FOLLOW-UP	1929-1944		1945-1949		1950-1955	
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
1. Alive without cancer	6	60	7	50	33	86
2. Alive with cancer in the neck	—	—	3	22	1	3
3. Alive with distant metastases	—	—	—	—	—	—
4. Expired with proved metastases or persistent tumor in the neck	1	10	1	7	1	3
5. Expired, cause of death unknown	1	10	1	7	1	3
6. Expired of other causes with no demonstrable tumor	—	—	1	7	—	—
7. Lost to follow-up	2	20	1	7	2	5
Total	10	100	14	100	38	100

has local persistence of cancer in the neck. At present good therapeutic results have been achieved in 46 of the 62 cases (74 per cent). Since 33 of these cases were recent ones, further follow-up will undoubtedly reduce this group of satisfactory results.

Of the patients known to have died of papillary thyroid cancer all had locally far-advanced lesions at the time of initial treatment. Invasion of trachea, thyroid cartilage, and so forth precluded a really curative operative procedure. The microscopic pathology in these cases did not differ significantly from the other cases.

DISCUSSION

It is apparent that despite the relatively benign nature of this neoplasm the heterogeneous treatment used in the management of these 62 patients was not remarkably successful in effecting cure. While an attitude of conservatism in treating this neoplasm has been encouraged by some,[2] it is questionable whether or not, in view of the low mortality and morbidity incident to the more radical procedures, it is more conservative to do multiple inadequate operations than a single radical procedure. For example, one patient who is known to us but who has never been treated at this hospital and consequently is not included in the present series was first operated upon in 1929 when a lymph node in the superior deep cervical lymph node chain was excised. Subsequently 6 secondary "conservative" operations have been performed for the same tumor in different portions of the neck. She is still alive with persistence of papillary cancer in the neck but without evidence of distant metastasis. The definition of "conservative" as here applied is certainly in doubt!

Difficulty in establishing an accurate clinical diagnosis makes it impossible to bypass pathologic confirmation before considering therapy. In this regard, as previously stated, the use of frozen section technique for immediate pathologic study is of value, and pathologists should be encouraged to increase their experience with its application in thyroid disease. When the diagnosis of papillary carcinoma of the thyroid has been established, the factors previously demonstrated by others and confirmed in this study should be used to guide the surgical plan.

In the management of the primary lesion the possibility of multiple foci of origin must be considered. In this study the opposite lobe was involved in 8 of 25 cases subjected to careful pathologic study. It is seldom that the surgeon can be certain of the absence of such foci on gross examination with the lobe visualized but otherwise undisturbed. Balanced against this possibility is the danger of injury to recurrent laryngeal nerves and, of greater import, the risk of total parathyroidectomy when total thyroidectomy is performed.

The incidence and distribution of lymph node metastases are most important considerations in planning therapy. Since in this series lymph nodes were

not removed in many cases, the incidence of metastases in 42 per cent is much lower than that reported by others. Frazell and Foote[5] in their study found the incidence to be 96 per cent when clinical evidence or suspicion of metastasis existed. In clinically negative cases the incidence was 61.2 per cent. In his series Crile[1] found lymph node metastases in 74.8 per cent of cases. The distribution of involved lymph nodes was also studied by Frazell and Foote;[6] the deep cervical (jugular) lymph node chain was most frequently involved, but no zone was free of involvement including the superior mediastinum. The frequency of spread to the latter is not sufficient to warrant routine splitting of the sternum and superior mediastinal dissection, a procedure described by McClintock and associates[7] for use when metastases to the superior mediastinal lymph nodes are suspected. Comparison between the so-called prophylactic group and the therapeutic group also showed a much greater tendency for involvement of multiple levels in the latter group. In our own material, in cases with a single palpable node, pathologic study of the specimen following neck dissection usually showed diffuse involvement out of all proportion to the clinical findings.

In the initial management of the lesion as it presents to the surgeon would seem to lie the success or failure of treatment. In this group of cases, all patients except one who were seen initially with a tumor found at the operating table to be resectable for cure are now alive and free of clinically or radiographically detectable tumor. The one exception is a woman who was subjected to repeated local excisional operations. Of our 7 patients who are either alive with persistent cancer or dead as a result of the tumor, 2 were seen initially after several previous attempts at local excision of the tumor, while 5 presented with far-advanced disease considered to be beyond the limits of the operation. We would then advocate the early and adequate treatment of the primary neoplasm. While it is impossible to describe a plan of management to fit all situations the following seems justified.

1. When operating upon a lesion of the thyroid gland, suspected of being a neoplasm, one should resect the entire involved lobe by extracapsular dissection. If the tumor involves the isthmus or the opposite lobe, then a wide margin should be taken about the area of extension. The management of invasion of contiguous structures in the neck challenges the skill and ingenuity of the surgeon. Although tracheal invasion generally forewarns of an unsuccessful resection, it is occasionally possible to take several tracheal rings to which the neoplasm is fixed, peeling these off the underlying mucosa which is left intact. The wall of the esophagus may be resected and closed primarily. Invasion of the carotid arterial system may be managed by resection and graft replacement or, as Frazell has indicated, by excision of the vessels. This means, of course, that all solitary nodules of the thyroid would be handled by total lobectomy. The hazards of such a procedure on one lobe are limited to damage of the recurrent laryngeal nerve. This nerve should be dissected and positively identified throughout its course in the thyroid area. It is mandatory that all who would operate upon the thyroid gland be intimately familiar with

the detailed anatomy and variations of this nerve as so clearly defined in publications such as that of Morrison.[10] The fear of its injury has prompted, in some instances, the advocation of subtotal resection of the gland or even of nonoperative therapy to the tumor. This is not justified. The experienced surgeon should be able to perform total extracapsular lobectomy with an incidence of permanent laryngeal nerve palsy of less than 5 per cent. If the nerve runs through the tumor it must be resected if cure is to be achieved.

2. Should a diagnosis of papillary carcinoma be made, a subtotal resection of the opposite lobe leaving only a small amount of normal glandular tissue on the posterior capsule should be performed. Great care must be taken to preserve viable parathyroid gland and the recurrent nerve must be carefully identified. The incidence of hypoparathyroidism attendant upon a bilateral total lobectomy does not, in our opinion, justify this procedure when one is dealing with papillary carcinoma unless involvement of both lobes is massive. Then total thyroidectomy is necessary.

3. In the presence of palpable lymph node metastases, one should proceed with a definitive neck dissection. Such palpable metastases are most commonly encountered beneath the sternocleidomastoid muscle. Therefore, in most instances, this will mean a "standard" radical neck dissection with sacrifice of the sternocleidomastoid muscle and internal jugular vein as described by George Crile, Sr. The frequent presence of this neoplasm in the young woman, and in children brings up the problem of the cosmetic result of neck dissection. The modification of the standard radical neck dissection by preservation of the sternocleidomastoid muscle previously mentioned[8] may in many instances be a satisfactory solution to this problem. Although we have not as yet encountered a metastasis to the submaxillary nodes, in view of the reported involvement of nodes in this triangle, it is now our practice to include it in the neck dissection.

4. Following the diagnosis of metastatic papillary carcinoma by excision of a node in the neck, in the absence of a clinically obvious tumor in the thyroid, one should perform a total lobectomy on that side and a subtotal lobectomy on the contralateral side, with an en bloc radical neck dissection on the side with demonstrable metastases. When such node excisions or biopsies have been done, the incision should be included in the en bloc resection. We have seen 2 patients with papillary carcinoma of the thyroid which had recurred in the scar of a previous operation.

5. If in the course of follow-up it becomes apparent that disease persists in the neck, secondary surgical removal may still control the tumor. Particularly is this true when the persistence is in a lymph node rather than diffusely invading the remaining vital structures of the neck. Irremovable or metastatic lesions should be treated with thyroid hormone, in dosage of 180 to 300 mg. per day, in view of the promising early experience with this substance. X-ray therapy may control the pain from osseous metastases and promote recalcification and healing in pathologic fractures. Radioactive iodine has been of little value in papillary carcinoma in our experience.

SUMMARY AND CONCLUSIONS

1. Sixty-two patients with papillary carcinoma have been studied. The presenting symptoms, diagnosis, pathologic findings, treatment, and end results judged by follow-up are reviewed.

2. The usual presenting symptom is a nodule in the thyroid, with or without enlarged lymph nodes. In some cases lymph node enlargement alone may be present. Thyrotoxicosis appears to have no significant relationship to this tumor.

3. The diagnosis may be suspected clinically under certain circumstances, but in all cases pathologic confirmation is necessary. Frozen section should be employed and may be of value in the immediate pathologic diagnosis.

4. There is no correlation between minute variations in microscopic pathology and prognosis.

5. Local excisional therapy was frequently but not invariably associated with local persistence.

6. Papillary carcinoma of the thyroid is a potentially lethal tumor.

7. In planning treatment the frequency of multiple foci of origin, lymph node metastases, morbidity from sacrifice of both recurrent laryngeal nerves, and complete parathyroid removal must all be considered.

8. Suggestions for surgical treatment are given based upon these considerations, but a single standard approach which will equally fit all situations does not appear feasible at this time.

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THE CHANGING PATTERN OF THYROID DISEASE

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IN OUR attempts to determine and fix in our minds certain values or percentage figures for the incidences of various diseases, we may overlook the fact that the diseases themselves may not be static but subject to change. Such seems to be the case in afflictions of the thyroid gland. This study, begun in an attempt to arrive at a reasonably accurate figure for the frequency of malignancy of the thyroid at the Augustana Hospital, was extended to cover all forms of thyroid disease encountered at surgery over a 20-year period. We have been fortunate at this institution to run a fairly consistent level of thyroidectomies and of significant number to lend credence to the trends shown. The years studied included 1935 through 1954. The cases analyzed totaled 4,542 with a yearly average of 226 and a range from 134 to 355.

The material was classified according to an outline set forth by the American Society for the Study of Goiter (now the American Goiter Association) and included the following: nontoxic nodular, toxic nodular, nontoxic diffuse, and toxic diffuse goiters, thyroiditis, adenomas, and malignant lesions (Table I). This division is clinical and pathologic in basis and requires a preoperative evaluation of the patients' toxicity followed by the surgeons' and pathologists' description of the gross and microscopic appearance of the gland. For purposes of clarity and simplification, the nodular and diffuse goiters have been charted separately from thyroiditis and the benign and malignant tumors. Their varying levels of incidence have been plotted at yearly intervals, using percentages to avoid projected errors from absolute figures. This was necessary because no 2 years had exactly the same number of thyroidectomies. The results are seen in Fig. 1.

NONTOXIC NODULAR GOITER

Early in the study the number of cases of nontoxic nodular goiter was relatively small. Since 1946, however, it has been the commonest type of goiter operated upon. In the last 2 years of study this goiter surpassed all other types combined. There was a total of 1,281 cases in the 20-year period, 383 occurring in the first decade and 898 in the second. The average age of these patients was 45 years, with a tendency for the yearly averages to gradually increase. For example, the average in 1935 was 40 years; in 1944 it was 43 years; and in 1954 it was 48.6 years. Eighty-six per cent were found in women.

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TOXIC NODULAR GOITER

Conversely to the nontoxic nodular goiter, the percentage of toxic nodular goiter decreased in a fairly consistent fashion throughout the study. At present we see more patients with toxicity due to Graves' disease than due to degenerating adenomatous tissue. There was a total of 1,593 in the entire series, with 1,097 in the first decade and 496 in the second. These patients averaged 50 years of age, and this remained remarkably consistent throughout the study. Ninety per cent were found in women.

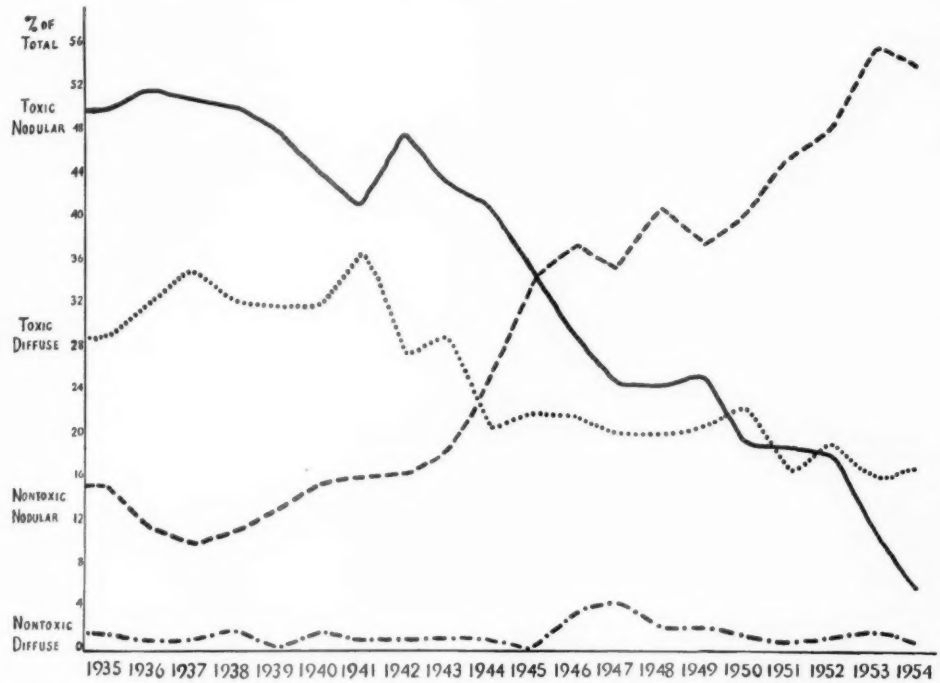

Fig. 1.—The distribution of toxic nodular, toxic diffuse, nontoxic nodular, and nontoxic diffuse goiters plotted yearly over the 20-year period of the study.

This reversal in predominance of the nontoxic over the toxic in more recent years is an interesting fact to speculate on. Two factors are certainly worth consideration for the increase of the nontoxic group. The first is economic. The years 1935 through 1944 were largely ones in which the prosperity of the country was at a low ebb, and, as a result, patients did not seek medical advice with the ensuing costs unless they were sick. The mere presence of a lump in the neck did not prevent an individual from doing his work, and, unless nervousness, palpitation, or more hampering symptoms supervened, it is likely that many ignored its presence. With greater prosperity, financial security, and increased participation in prepaid insurance plans, the ability to afford medical care may have encouraged patients to investigate lesions previously slighted.

The second factor is that of cancer consciousness not only on the part of the surgeon but the public as well. The education of the public by means of newspapers, radio, and more recently television, with reference to the presence of tumors, has been tremendously increased in the latter division of the study.

TABLE I. DISTRIBUTION OF TOTAL MATERIAL BY YEARS

CLASSIFICATION	1935-1944										
	1935	1936	1937	1938	1939	1940	1941	1942	1943	1944	10-YEAR TOTAL
Nontoxic nodular	21	26	25	21	29	33	34	39	66	89	383
Toxic nodular	67	113	125	94	106	94	87	113	152	146	1,097
Nontoxic diffuse	2	2	3	4	1	4	2	3	5	4	30
Toxic diffuse	39	70	87	61	70	67	78	64	103	73	712
Thyroiditis	1	5	1	2	5	5	1	4	4	7	35
Adenomas	2	1	2	2	6	4	5	6	15	25	68
Malignancy	2	1	3	4	4	4	3	6	5	11	43
Carcinoma	(2)	(1)	(3)	(4)	(3)	(4)	(2)	(6)	(4)	(8)	(37)
Recurrent carcinoma							(1)		(1)	(3)	(5)
Sarcoma					(1)						(1)
Total cases	134	218	246	188	221	211	210	235	350	355	2,368

	1945-1954											
	1945	1946	1947	1948	1949	1950	1951	1952	1953	1954	10-YEAR TOTAL	20-YEAR TOTAL
Nontoxic nodular	106	91	98	110	85	89	67	79	96	77	898	1,281
Toxic nodular	106	71	69	66	58	42	27	30	19	8	496	1,593
Nontoxic diffuse	1	9	13	6	5	3	1	2	3	1	44	74
Toxic diffuse	67	53	56	54	47	50	24	32	27	24	434	1,146
Thyroiditis	3	5	10	7	15	14	9	9	12	12	96	131
Adenomas	18	6	22	13	7	9	6	5	7	9	102	170
Malignancy	4	9	11	12	10	14	12	8	10	14	104	147
Carcinoma	(4)	(8)	(11)	(10)	(10)	(12)	(9)	(5)	(8)	(11)	(88)	(125)
Recurrent carcinoma		(1)		(1)		(2)	(2)	(2)	(2)	(3)	(13)	(18)
Sarcoma				(1)			(1)	(1)			(3)	(4)
Total cases	305	244	279	268	227	221	146	165	174	145	2,174	4,542

The fear that they may be harboring a cancer and the knowledge that it may be cured if treated early has been repeatedly reflected in the histories taken in the second decade. Probably of greater importance has been the change in thinking among the surgeons themselves, who in recognizing the hopelessness of carcinoma of the thyroid when diagnosed preoperatively have broadened their surgical indications to include nodular glands which by no other criteria than their nodularity might conceivably harbor an incipient malignancy or its precursor.

NONTOXIC DIFFUSE

In every year of the 20 studied, there was at least one case which was diagnosed preoperatively as a nontoxic nodular goiter but which on gross examination proved to be a diffuse enlargement. This enlargement was not the soft elastic swelling of excess colloid as seen in the adolescent goiter. Instead the gland was firm, with prominent lobulations and in patients averaging 40.4 years of age. Microscopically, they presented a varying picture of hyperplasia, lymphocytic infiltration, and increased fibrosis. Some of these demonstrated sufficient numbers of lymphocytic elements with follicles to suggest a very early thyroiditis. In others the follicular hyperplasia was such as to suspect an incipient or burned out Graves' disease. None of these patients were believed to have toxic diffuse goiter; only one was young enough to be considered adolescent; and all were operated upon with the impression of nodularity in the gland. The result is a group which does not fit the confines of the outline well, but nonetheless exists. There were 74 of these cases, 30 occurring in the first decade and 44 in the second. No specific trend appeared in reference to its incidence.

TOXIC DIFFUSE GOITER

Toxic diffuse goiter (Graves' disease, exophthalmic goiter, primary hyperthyroidism) was seen to decline moderately but definitely over the 20-year period. A total of 1,146 were seen in the entire study, with 712 falling in the first 10 years and 434 in the second. The average age of these patients was 36.9 years; 84 per cent were women.

The reason for the decline of this disease cannot be stated unequivocably, but again increased iodine consumption may be a factor. Although we have used the thiouracil compounds for the preparation of the patient for surgery and not a substitute for surgery, and radioactive iodine has been advocated in a very limited number of cases, it is conceivable that patients ordinarily referred for surgery may have been treated medically elsewhere. However, it will be noted that aside from the unusually large number in 1941, the decline has been a reasonably steady and continuous one over the entire study and not punctuated by precipitous drops at points where these agents might be expected to have effected the curve.

THYROIDITIS

In the entire series, 131 cases of primary thyroiditis were reported. In these glands the thyroiditis was the predominant pathology. In cases in which

lymphocytic infiltration or fibrosis appeared rather spottily and in small amounts, the term secondary thyroiditis might be appended to the main diagnosis on the pathologist's report but these were not included in the grouping. Of the 131, 4 were diagnosed as being subacute thyroiditis. These 4 patients variously reported symptoms of fever, sore throat, dysphagia, and tenderness over the gland. Microscopically, the characteristic findings were those of degeneration of the follicular epithelium associated with acute and chronic inflammation, proliferation and regeneration of the follicles, and the presence of large numbers of foreign-body giant cells. This condition of the thyroid has been well documented by DeQuervain and Giordanengo[4] and is known under the names of subacute, granulomatous, or giant-cell thyroiditis. The etiology is unknown but the dramatic response to cortisone should eliminate the need for surgical diagnosis.

The remaining 127 cases fall into a classification which is suffering from nomenclatural growing pains and at the present a member of this group might be called chronic thyroiditis, Hashimoto's struma, lymphoid goiter, struma lymphomatosa, lymphadenoid goiter, lymphoid-epithelial goiter, lymphocytic goiter, Heidel's struma, or fibroinvasive goiter, to name only some of the possibilities. These goiters were usually diffusely, symmetrically, but only moderately enlarged. Not infrequently there was adherence in some degree to the surrounding cervical structures. Most were pale in color and firm to hard in consistency. Microscopically, the picture varied chiefly in the proportion of epithelial, lymphoid, and fibrous tissue elements. In some the lymphoid infiltration was in extreme abundance with large lymphoid follicles and clear germinal centers filling the microscopic field. In others the picture was one of almost total fibrous replacement with a scattering of lymphocytes. The average age of these patients was 42.7 years, and of the 127 only 6 were men.

We had no cases which on the basis of gross fibroinvasive qualities or histology differed so markedly from the extremes seen with lymphoid goiter to merit a separate classification as Reidel's struma. With the former, slight adherence to the strap muscles is not uncommon and in no instance was the picture so exaggerated or extensive as to render the case inoperable. It was with more certainty that we could conclude that chronic thyroiditis or lymphoid goiter was increasing in frequency. Thirty-five cases were seen in the years 1935 through 1944, and 96 from 1945 through 1954. The reasons for this are as obscure as the various proposed etiologies for the condition.

ADENOMA

In the 20-year period, 170 benign adenomas were found. The criteria used to separate these true neoplasms from the nodules of adenomatous goiters were similar to those outlined by Lahey.[6] These included encapsulation, homogenous structure, variation from the structure of the thyroid beyond the capsule, and evidence of compression of adjoining thyroid tissue by the adenoma. The basic grouping into follicular and papillary types was dependent upon the formation,

or attempted formation, of follicles or papillae by the lesion. If follicular development was so rudimentary as to result in cords or columns of cells, the lesion was described as embryonal. If very small follicles predominated the lesion, it was listed as fetal. The few that were mainly composed of the large acidophilic cells called Hürthle cells were so named. In those instances where a mixed picture of 2 follicular elements or papillary and follicular existed, the predominant growth pattern was used in the final diagnosis. The average age of these patients was 42.6 years and 89 per cent occurred in women. In the first decade 68 benign adenomas were removed and in the second, 102. The follicular lesions considerably outnumbered the papillary in both decades (Table II).

TABLE II. DISTRIBUTION OF BENIGN ADENOMAS

	1935-1944	1945-1954	TOTAL	PER CENT
Follicular	61	93	154	90.5
Embryonal	2	11		
Fetal	55	77		
Hürthle cell	4	5		
Papillary	7	9	16	9.5
Total	68	102	170	100.0

MALIGANT LESIONS

A total of 147 of the surgical specimens were diagnosed as being malignant. Of these, 129 were new cases and 18 were recurrent. The material was listed under 6 headings as may be noted in Table III. Adenoma with malignant change (adenoma malignum, malignant adenoma) was present in 11 instances and included those adenomas which showed very early evidence of altered cell structure and arrangement and, frequently, blood vessel invasion. Papillary carcinoma was diagnosed 42 times and included those tumors having a papillary structure as the dominant feature and in the greatest amount if a mixed lesion was present. Adenocarcinoma was the term used to include those malignant lesions which presented a follicular arrangement or anything remotely suggestive of such a pattern. We had 43 cases forming 33.3 per cent of the total in this category. This percentage is slightly higher than figures more commonly quoted[2, 5, 7] but stems more, we feel, from the various ways tumors are classified rather than any inherent differences in material seen. Undifferentiated carcinoma was listed in 27 instances and included those tumors made up of small cells, giant cells, spindle cells, and in addition those demonstrating squamous metaplasia to an extent to suggest epidermoid carcinomas. Hürthle-cell carcinoma was diagnosed in 2 lesions and, as in adenoma, were so named because of the predominating presence of Hürthle cells. Sarcoma was found in 4 cases; 3 were labeled lymphosarcoma and one fibrosarcoma. The microscopic picture in the first may be very difficult to differentiate from small cell carcinoma and at times even simulates lymphoid goiter in appearance. A careful follow-up is invaluable in forming the ultimate diagnosis, for the carcinomas are usually rapidly fatal, whereas patients with lymphosarcoma may survive for a surprisingly long period of time. Although described by some authorities[9] as the

commonest nonepithelial malignant tumor of the thyroid, we found only one fibrosarcoma in the series. The average age of the patients in this group of malignant thyroid tumors was 49.8 years; the percentage in women was 85.

TABLE III. DISTRIBUTION OF MALIGNANT TUMORS

TYPE MALIGNANT	1935-1944	1945-1954	TOTAL	PER CENT
Adenoma with change	3	8	11	8.5
Papillary carcinoma	13	29	42	32.6
Adenocarcinoma	10	33	43	33.3
Undifferentiated	11	16	27	20.9
Hürthle cell	0	2	2	1.6
Sarcoma	1	3	4	3.1
	38	91	129	100.0

It has been demonstrated in other studies[1, 3, 8] that carcinoma of the thyroid occurs less commonly in either toxic goiters or in diffuse goiters but with increased frequency in those glands possessing single adenomas. Our material substantiated the first 2 premises and also the third in the relatively few cases in which we could demonstrate a single adenoma. But because single adenomas of any type proved to be the exception rather than the rule in our material, it assumed a minor role in the preoperative evaluation of malignancy or in the decision for surgery itself. In arriving at a figure for the incidence of thyroid cancer in our surgical material, we may by a process of elimination of diffuse goiters and toxic goiters and multinodular goiters (in contradistinction to single adenomas) come up with a frighteningly high figure of 14 per cent. If, on the other hand, we included all goiters—diffuse, toxic, and nodular, and eliminate all malignant tumors which may have been suspected preoperatively, the incidence can be lowered to a more reassuring 2.1 per cent.

The incidence of cancer (both suspected and unsuspected in all types of goiter) in the first 10 years was only 1.6 per cent, while in the second 10 years, is was more than doubled to 4.2 per cent. To suggest that cancer of the thyroid was actually increasing on the basis of the increased number encountered at surgery in the last 10 years would overlook the concomitant rise of nontoxic nodular goiters in the same period. The ratio of nontoxic nodular lesions and malignant lesions has changed only slightly and probably not significantly. In the first 10 years the incidence of cancer in nontoxic nodular goiter was 9.5 per cent; in the second 10 years it was 9.9 per cent. Therefore, we may assume that although we are encountering many more cases of cancer of the thyroid in surgery today, its actual frequency in the type of goiter with which it is most often confused has remained static. It should also be noted that a preoperative suspicion of cancer was present in 14 of the 38 cases in the first half of the study and 20 of the 91 in the second (26 per cent). If we subtract these cases from the total, we find that the incidence of unsuspected cancer in nontoxic nodular goiter was 6.7 per cent or one in every 15 cases operated upon.

The increase in new cases of carcinoma was reflected in the parallel increase in recurrent cancers. Five cases were seen in the first 10 years, 13 in the second (Table IV). Of this total of 18 cases, 13 were papillary carcinoma, 4

adenocarcinoma, and 1 undifferentiated carcinoma. The recurrence rates of these different types roughly scale the inverse portion of their type of malignant tumor to their likelihood of survival. The patients with the less malignant papillary lesions lived to have local recurrences and repeated operations, while the patients with anaplastic tumors more commonly developed distant metastases or rapid local invasion and died. The patients with adenocarcinomas did a little of both.

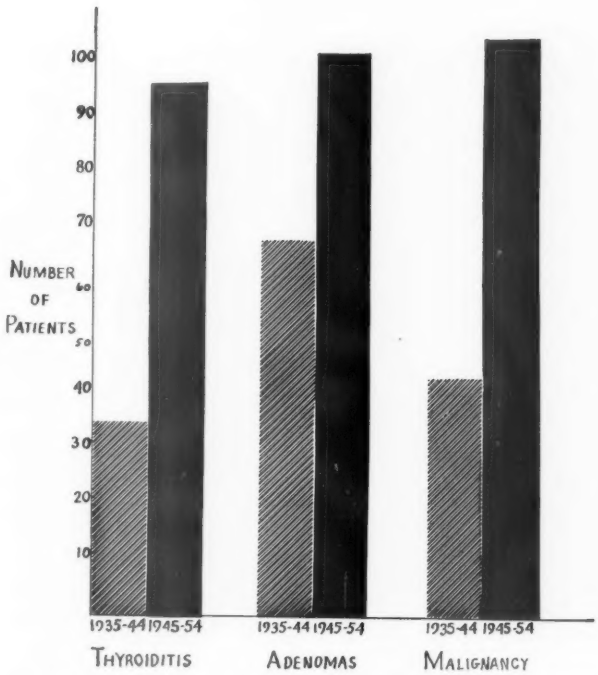

Fig. 2.—Comparative distribution of thyroiditis, adenomas, and malignancy in the first and second decades of the study.

TABLE IV. DISTRIBUTION OF RECURRENT CARCINOMA

TYPE	1935-1944	1945-1954	TOTAL
Papillary carcinoma	3	10	13
Adenocarcinoma	2	2	4
Undifferentiated	0	1	1
Total	5	13	18

SUMMARY AND CONCLUSIONS

A 20-year period of thyroid surgery at the Augustana Hospital, representing 4,542 cases was analyzed. During this period, trends in the incidence of the various types of thyroid disease were noted. Although nodular goiters were operated upon with about the same frequency over the entire study, the ratio of toxic to nontoxic cases reversed. A gradual but definite decline in the number of toxic diffuse goiters was seen. Chronic thyroiditis or lymphoid goiter increased in frequency. Despite the apparent increase in incidence of malignant tumor when compared to all types of goiter, its incidence as compared to nontoxic nodular goiter did not change. This fact suggests a partial reason for the

discrepancy in cancer incidence noted in the literature. The incidence of unsuspected cancer in nontoxic nodular goiters operated upon in the period of this study was 6.7 per cent.

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AN EVALUATION OF HYPAQUE SODIUM (WIN 8308-3) FOR CEREBRAL ANGIOGRAPHY

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SINCE the acceptance of cerebral angiography as a safe diagnostic procedure, the merits of various media and the techniques of their administration have been reported. The purpose of this study was to evaluate Hypaque sodium (WIN 8308-3), in both animals and patients, as a contrast medium and to compare it with other media currently in use, that is, Diodrast, Thorotrast, Urokon, and Renographin.

METHODS AND MATERIALS

Twenty-two dogs were used in this study. Under Nembutal anesthesia, polyethylene catheters were placed in the femoral vein and carotid artery. Injections of the various contrast media were made via the carotid catheter, with variations in amount, concentration, and rate of injection. Then, following the method of Broman and Olsson,[2] 100 c.c. of a 0.5 per cent solution of trypan blue was given via the femoral vein over a 10- to 15-minute interval. After the injection of the dye, the cerebral vessels were flushed with 200 to 300 c.c. of saline and the animal immediately perfused with 10 per cent formalin for fixation. Following perfusion, the cranium was removed and the dura opened. The head, with the exposed brain in situ, was immersed in fresh 10 per cent formalin for 24 hours after which time the brain was removed intact, sectioned, and examined.

Observations were made upon the blood pressure, pulse, respirations, and pupil size during and immediately following the injections.

The radiographic densities of similar concentrations and amounts of the various media were compared.

Since the evaluation of the laboratory data, percutaneous carotid angiography has been performed on 580 patients using Hypaque as the contrast medium. Initially, 6 c.c. of a 25 per cent solution was used per injection. Eventually, a 50 per cent solution was used in all cases, in quantities of 10 to 12 c.c. per injection; 4 such injections were required for bilateral carotid angiographic study. Either local or sodium Pentothal anesthesia was employed in the procedure. Observations were made on the patients during and following the injections.

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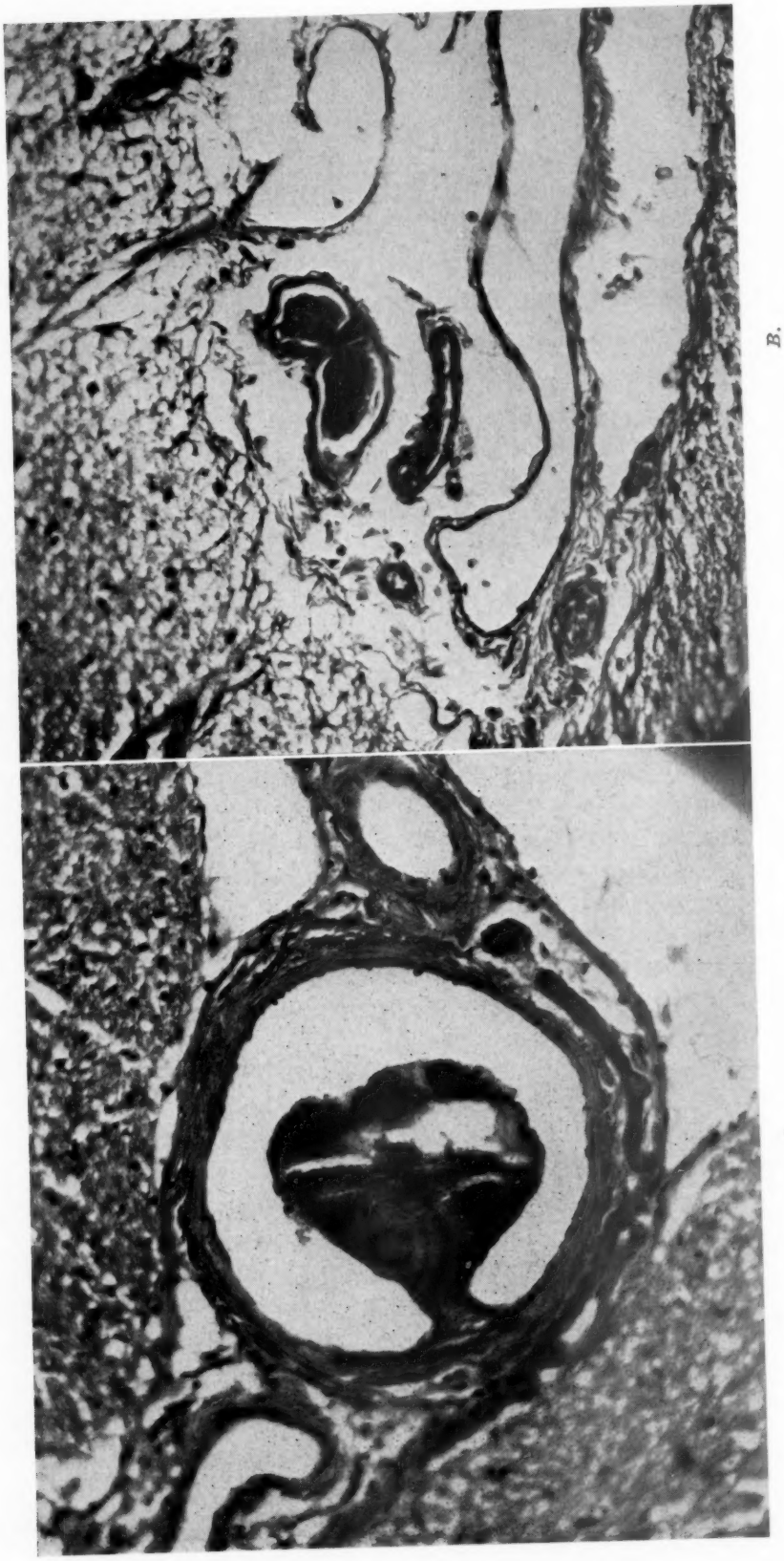

B.

A.

Fig. 1.—*A*, and *B*, Recent thrombi found in brains of animals receiving Diodrast and Urokon. (×280.)

RESULTS

Animal Experiments.—The immediate effects of rapid injection of Hypaque into the carotid artery of the dog were (1) transient apnea followed by temporary increase in respiration, (2) temporary slowing of the pulse, (3) temporary dilatation of the pupil on the side of the injection, and (4) occasional movements of the facial musculature. These effects were also observed when other media were employed and varied in degree with the different media and their concentrations.

Animals were given Hypaque in amounts varying up to 4 injections of 20 c.c. each. In none was there gross staining by trypan blue in the cut sections of the brains. In the brains of the animals receiving Diodrast and Urokon, gross staining was present, often limited to the side of the injection. The amount of staining varied with the amount and concentration of material used. Minimal staining was observed in the brains of animals receiving Renographin, and no staining was seen when Thorotrast was used. Engorgement of the blood vessels, particularly in the region of the basal ganglia, was a common finding following the use of any of the media, provided adequate amounts and concentrations were employed. This effect was most marked in the brains of the animals receiving Diodrast and Urokon.

To date, sampling of some of the brains for microscopic study has been done, including sections from the brains of animals receiving each of the media employed. In the brains of animals receiving Diodrast (70 per cent), Renographin (76 per cent), and Urokon (50 per cent), recent thrombi were found in some of the arterioles. Fig. 1 illustrates this finding. Because of the short time interval between the injection of the contrast medium and perfusion of the animal, other evidence of vascular damage was not demonstrated. In the brains of animals receiving lesser concentrations of the above media, definite staining reactions were present, but thrombi were absent. Nor were thrombi seen in the brains of the 2 animals receiving the greatest amounts and concentrations of Hypaque. The maximum amount of Hypaque used in any single animal experiment was 4 injections of 20 c.c. each of 50 per cent Hypaque.

The radiographic density of 50 per cent Hypaque compared favorably with that of Thorotrast. Because of the necessity for using lesser concentrations of Diodrast, Urokon, and Renographin, the contrast densities of these media were considerably less than either Thorotrast or Hypaque.

Clinical Aspects.—Percutaneous carotid angiography was performed on patients in all age groups with satisfactory visualization of the cerebrovascular system. Fig. 2 shows a preoperative angiogram using Thorotrast as compared with a postoperative angiogram on the same patient using 50 per cent Hypaque.

Most of the angiograms were done using 2 injections of 10 c.c. each of 50 per cent Hypaque for each side injected. Occasionally, larger amounts were used for better visualization of a lesion. Fig. 3 illustrates angiograms using first 10 c.c. and then 20 c.c. to demonstrate more clearly the lesion.

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Fig. 2.

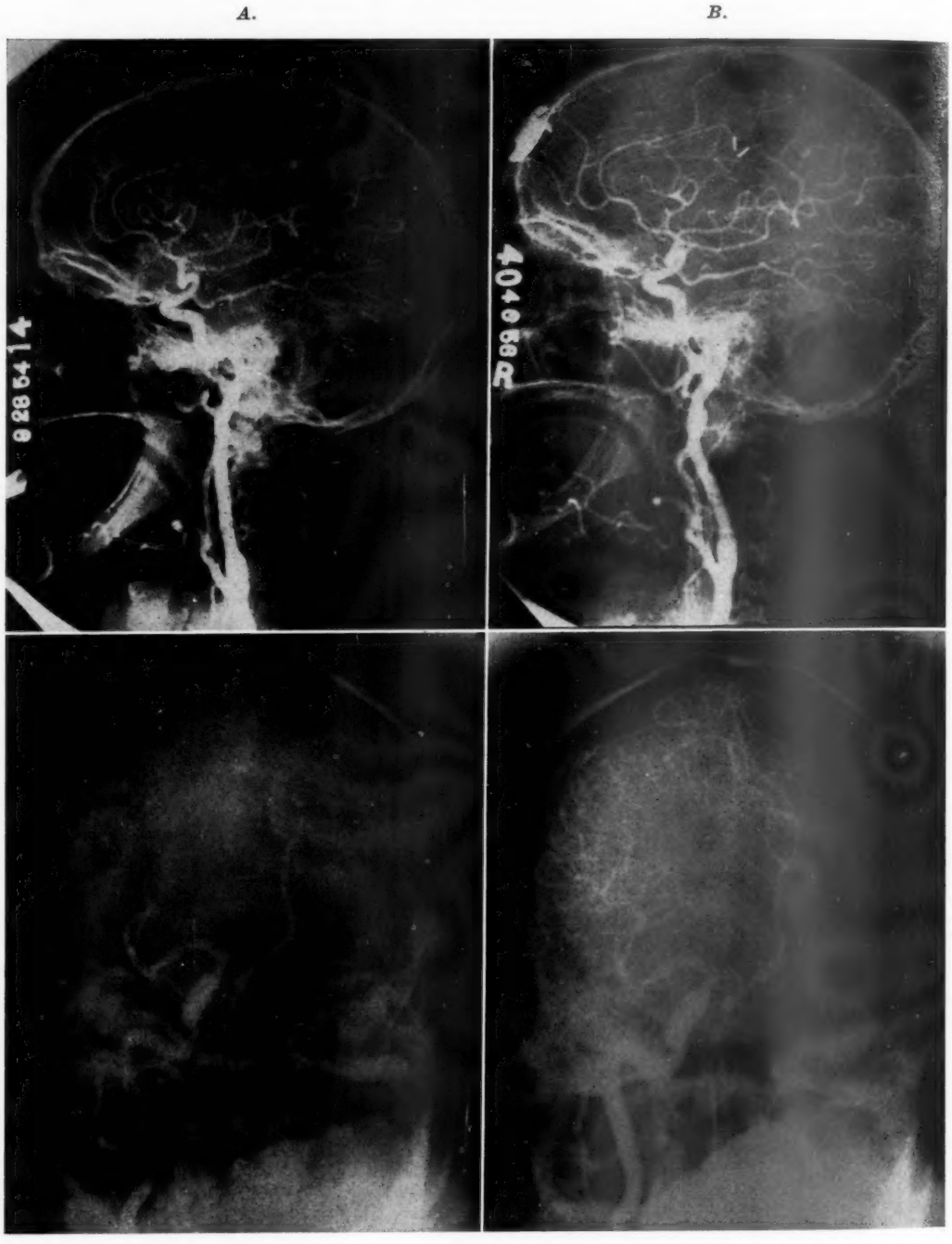

Fig. 3.

Fig. 2.—*A*, Preoperative angiogram using 10 c.c. Thorotrast. *B*, Postoperative angiogram using 10 c.c. Hypaque. Same patient as in *A*.

Fig. 3.—*A*, Angiogram using 10 c.c. Hypaque. *B*, Angiogram on same patient as in *A*, using 20 c.c. Hypaque.

No complications have occurred from the use of larger quantities of Hypaque. The use of larger quantities of this contrast medium lends itself to the employment of single exposure technique. When the Fairchild camera or other multiple exposure techniques are used, much smaller amounts give satisfactory studies.

All patients were skin tested with Hypaque prior to angiography and no responses contraindicated the use of the medium. There were no clinical manifestations of allergic responses to Hypaque. This is in agreement with observations made by Lowman and co-workers[6] in their experience with Hypaque in excretory urography.

The effects of the rapid injection of Hypaque into the carotid arteries of patients were evaluated when the procedure was done under local anesthesia. The patients were questioned regarding pain and discomfort during and immediately following the injections. A majority complained of some paresthesias or dysesthesias over the face and scalp (mainly a burning pain), usually on the side of the injection. This was accentuated when a thrombosis of the internal carotid artery was present and the medium was shunted into the external carotid artery.

Recently we have observed that when the procedure is done under local anesthesia, there is, in some patients, an associated fall in the systemic blood pressure within a few minutes following injection of the contrast medium. This effect has not been observed when Pentothal anesthesia was employed; rather, the reverse is true, that is, the blood pressure tends to rise somewhat following the injection. In several patients in whom this hypotensive effect was observed, a more dilute solution (25 to 35 per cent) was used and the blood pressure effect was either reduced or absent. Contrast density in these angiograms was satisfactory, and the discomfort during the injections was less.

Two patients expired within 12 hours following angiography. One, a 16-year-old white boy, was admitted shortly after the onset of sudden hemiplegia. An angiogram using 2 injections of 6 c.c. each of 25 per cent Hypaque was normal. The patient expired suddenly 11 hours later. At autopsy, a large acute parietal lobe hematoma was found not visualized in the angiogram. A second patient, a 34-year-old white woman, died 6 hours after a vertebral angiogram using Hypaque. The autopsy showed a complete occlusion of the basilar artery with atheromatous plaques. A third patient, a 34-year-old Negro woman, developed a unilateral facial weakness following angiography, which disappeared after 2 days. A fourth patient, a 36-year-old white man, who was admitted with a diagnosis of subarachnoid hemorrhage confirmed by lumbar puncture, had a generalized convulsion following an injection with Hypaque. The angiogram of this patient was normal.

DISCUSSION

Angiographic studies obtained with the use of Hypaque as the contrast medium were of excellent contrast quality. The radiographic density is less

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than that obtained with Thorotrast, but superior to that obtained with safe concentrations of Diodrast, Urokon, or Renographin.

In a previous publication, we reported angiographic complications using Diodrast or Thorotrast in 5 patients in 215 studies.[5] All complications occurred in patients over the age of 60, suspected of having cerebrovascular disease. Fewer complications have occurred with Hypaque.

There is still the disadvantage of the discomfort at the time of the injection under local anesthesia. This may be reduced either by the use of lesser concentrations of the medium or by the use of smaller amounts per injection during multiple exposure technique.

SUMMARY

An experimental and clinical evaluation of Hypaque sodium as a contrast medium for cerebral angiography shows that it is superior to other media presently in use. Its superiority is based upon its tolerance by the patient at the time of injection, a high degree of radiographic density, and its safety in patients over the age of 50.

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A MODIFIED DE BAKEY HEART PUMP FOR USE IN EXTRACORPOREAL CIRCULATION

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IN THE development of the various extracorporeal circulation units a number of principles have been utilized in the design of the pumps. These include: (1) the bellows-type pump,[9, 23] (2) the DeBakey pump[4] or modification thereof,[10, 12, 14, 16-19] (3) the finger pump (most commonly the Sigmamotor pump),[1-3, 13, 15, 20] or (4) a pump such as the Dale-Schuster pump[5, 21] which uses alternate positive and negative air pressure and valves to propel the blood. Keitzer[11] demonstrated the utility of the modified DeBakey pump in the Leonard-Skeggs artificial kidney. A similar pump with a DeWall oxygenator[15] utilized in over 300 open cardiotomy experiments in dogs and in 12 intracardiac procedures in patients is the subject of this report.

To be used clinically a satisfactory pump must incorporate a number of qualities. Simplicity and reliability of construction and operation should preclude mechanical failure but allow ready access to tubing and adaptors adjacent to the pump. An explosion-proof motor with an excess of power will allow constant rates of flow despite changes in the blood pressure of the recipient. Intermittent propulsion will produce pulsatile flow and simulate heart action. Hemolysis is minimized if turbulent flow and foaming in the region of the pumping mechanism is eliminated. It is desirable for the pump to be readily disassembled, portable, and inexpensive.

The modified DeBakey pump (Fig. 1)* consists of a one-fourth H.P. explosion-proof motor (Fig. 1, *H*) to which are attached 2 rotating wheels supporting 3 rollers. Latex rubber tubing is stretched across these rollers and as the wheel rotates the tubing is partially occluded and the blood is propelled in a unidirectional fashion into the Tygon† tubing of the extracorporeal circulation. Tooled metal part-rings (Fig. 2) slip over the tubing and fit snugly into the holes on the base of the pump preventing any tendency for the tubing and adaptors to be pulled into the pumping area. Latex tubing, one-half inch in internal diameter, is used for tubes *A* and *B* and five-eighths inch for tube *C* (Fig. 1). Tube *A* conveys oxygenated blood to the patient. Tube *C* carries venous blood from the patient into the DeWall oxygenator. Blood aspirated from the opened heart and stored in a cardiotomy suction reservoir is propelled through tube *B* to join the main column of venous blood in tube *C*.

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*Model ACH 3 as manufactured by Kent Machine Company, 113 Portage Trail East, Akron, Ohio.

†Tygon tubing manufactured by U.S. Stoneware Co., 12 East Ave., Tallmadge, Ohio.

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Fig. 1.

Fig. 2.

Fig. 1.—Modified DeBakey pump showing details of tubing. Note unused space for fourth circuit. Entire pump shown in inset. *A*, Arterial circuit, *B*, cardiotomy suction circuit, *C*, venous blood circuit, *D*, base plate of pump, *E*, adaptor shunting cardiotomy-suction blood into main venous circuit, *F*, screw clamp regulating venous blood flow, *G*, vernier regulating r.p.m., and *H*, one-fourth H.P. motor.

Fig. 2.—Base plate. Note part-ring pulled out of tooled receptacle. Stainless steel adaptor joins Tygon to latex tubing.

A vernier located on top of the pump (Fig. 1, *G*) regulates the volume flow and allows preoperative calibration by adjusting the vernier until the desired arterial flow is obtained. The flow through the venous side at this point will exceed the arterial flow because of the greater diameter of the venous tubing. This is compensated for by placing a screw clamp on the venous side (Fig. 1, *F*) occluding the tubing until the venous and arterial flow are equal. Once this has been done no further adjustment is needed. The pump has a flow rate which varies from 0 to 4,000 c.c. per minute. This flow rate remains constant against pressure ranges of 0 to 300 mm. Hg.

All experiments in this series were conducted at 35 c.c. kilograms per minute. Flows in humans have ranged up to 100 c.c. kilograms per minute and in total volume up to 2,100 c.c. per minute.

In 10 mongrel dogs a 4 cm. long incision was made in the right ventricle and kept open for 30 minutes; total extracorporeal circulation time in these animals was at least 35 minutes. Serial determinations were made of the blood platelet count, the white blood cell count, and the serum hemoglobin. Blood samples were drawn after 5 minutes of extracorporeal circulation to allow for mixing of the patient's blood with that in the oxygenator and were drawn again at the end of 30 minutes. The results are summarized in Table I.

TABLE I. CHANGES IN SERUM HEMOGLOBIN, WHITE BLOOD CELL COUNT, AND PLATELET COUNT IN DOGS MAINTAINED ON HEART-LUNG MACHINE AT 35 C.C. PER KILOGRAM PER MINUTE DURING A RIGHT VENTRICULOTOMY, KEPT OPEN FOR 30 MINUTES

DOG NUMBER	SERUM HEMOGLOBIN IN MG. PER CENT AFTER 5 MINUTES OF PERFUSION	SERUM HEMOGLOBIN IN MG. PER CENT AFTER 30 MINUTES OF PERFUSION	INCREASE IN SERUM HEMOGLOBIN DURING PERFUSION	BLOOD PLATELET COUNT DECREASE DURING PERFUSION	WHITE BLOOD CELL COUNT DECREASE DURING PERFUSION
1	179	254	75	152,000	1,000
2	194	226	32	94,000	1,400
3	270.4	316	46	36,000	3,200
4	158	224	66	76,000	1,000
5	115	185	70	44,000	400
6	112	171	59	48,000	600
7	198	221	23	26,000	----
8	399	431	32	100,000	----
9	72	188	116	44,000	----
10	395	475	80	127,000	----
			Average increase 60 mg. per cent	Average decrease 75,000 per mm.^{3}	Average decrease 1,270 per mm.^{3}

The average increase in serum hemoglobin of 60 mg. per cent during the final 25 minutes of a 30-minute perfusion compares favorably with published reports of similar studies (Table II) performed with various pumps and oxygenators. Dog blood hemolyzes readily; the trauma of blood-letting accounts for much of the hemolysis in the "5-minute" specimen. The platelet decrease of 75,000 and the white blood cell decrease of 1,270 are within acceptable ranges when compared with other reports (Table II).

TABLE II. CHANGES IN SERUM HEMOGLOBIN, PLATELET, AND WHITE BLOOD CELL COUNTS NOTED BY VARIOUS AUTHORS IN EXPERIMENTAL ANIMALS EXPOSED TO RIGHT VENTRICULOTOMY AND EXTRACORPOREAL CIRCULATION OF APPROXIMATELY 30 MINUTES DURATION

AUTHOR	SERUM HEMOGLOBIN (MG. %)	PLATELETS	W.B.C.
Cross et al.[3]	10-160	Drop of roughly half	----------
Clowes et al.[2]	121-398	----------	----------
Dennis et al.[5]	19 (av.)	----------	----------
Dodrill et al.[6, 7]	100-150	50 per cent decrease	----------
Falor et al.	60 (av.)	50 per cent decrease	Transient fall
Kolff et al.[13]	195 (av.)	Transient fall	Transient fall
Kusserow[14]	150 (av.)	----------	----------
Melrose[17]	50 (per hr.)	25 per cent decrease	Transient fall
Miller[18]	93 (av.)	----------	----------
Osborn et al.[22]	Hemolysis slight	----------	----------
Wesoloski et al.[23]	136	----------	----------

CONCLUSION

A modified DeBakey pump, simple both in construction and as used in extracorporeal circulation, is described. An extensive experience has demonstrated the reliability of the pump and the relatively small degree of blood destruction associated with its use.

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THE TECHNIQUE OF IMPLANTATION OF THE INTERNAL MAMMARY ARTERY INTO THE MYOCARDIUM OF THE DOG

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WITH THE TECHNICAL ASSISTANCE OF BERYL KALLEMEYN, R.N.

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IN THE past 2½ years we have done 102 experiments in an attempt to assess the value of intramyocardial implants of the internal mammary artery in the functional replacement of the coronary artery circulation in normal dogs, and our results are being reported elsewhere. Four to 28 months after implantation we found that 89 per cent of our implants were blocked or badly stenosed inside or outside the heart. In our first 11 dogs which were autopsied we found the implants blocked in every case. Vineberg,[4] on the other hand, reported 46 per cent of successful implantations in normal hearts. We had been using our own (Pearl)* technique, which was kept under constant scrutiny to avoid technical errors which might contribute to the high rate of occlusion, and minor variations in technique were made as the project progressed. Chief among these was the elimination of any unnecessary trauma to the artery and the avoidance of angulation, torsion, or tension in its implantation. In view of our high incidence of occlusion in the implanted artery we prepared 2 new series of implants, one by the Pearl method and the other by the original Vineberg method. Details of this study will be set forth in another article. The Vineberg technique has been fully reported elsewhere.[3, 4] The purpose of this article is to present the technical aspects of our method of implantation.

In general, the Pearl method differs from the Vineberg method in the following respects. In the Pearl technique the entire internal mammary artery is freed of all its branches from its origin to the sixth or seventh intercostal space, and the mobilized artery is implanted into a tunnel in the deep one-third of the left ventricular myocardium with its end open in the tunnel. In the technique reported by Vineberg, the fourth, fifth, and sixth intercostal branches of the artery are cut between ligatures, leaving the second and third intercostal branches still attached; the main artery, ligated at its end, is then drawn through the myocardium so that the fifth or sixth intercostal branches, or both, are left open in the tunnel. In the Pearl technique the implant is anchored to the myocardium at the tunnel entrance; in the Vineberg procedure

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*For simplicity of description we designate the method which we employ as the "Pearl" method. This method adopts, with modifications, certain steps previously reported by Glenn and Beal.[2]

the ligated main artery is anchored at the tunnel exit. Vineberg is now ligating more branches of the internal mammary artery so as to allow a more direct course of the artery toward the left ventricle, but continues to ligate the main artery and to depend upon one or two intercostal branches to bring blood to the myocardium. We chose our technique because, according to the laws of hydrodynamics, we would expect a greater flow of blood from the open end of an artery with branches ligated than from the same artery with branches attached, and more blood flow from the open end of a main artery than from a smaller branch of the artery ligated at its end.

The technique which we use and recommend is as follows. With the dog on his right side, the left thoracic cavity is entered through the fifth intercostal space. The left internal mammary artery is freed of all its branches from its origin to below the sixth intercostal space, cutting the branches between ligatures of 5-0 silk (Fig. 1). The main artery is cut between ligatures at the

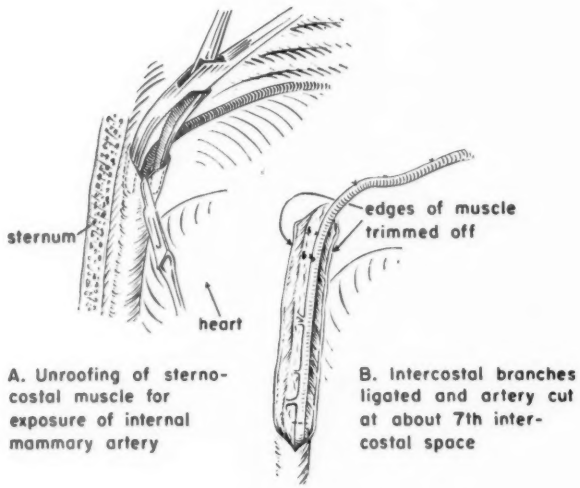
sternum
heart
edges of muscle
trimmed off
A. Unroofing of sterno-costal muscle for exposure of internal mammary artery
B. Intercostal branches ligated and artery cut at about 7th inter-costal space

Fig. 1.—Mobilization of artery.

sixth or seventh intercostal space and is dislocated so as to approach the heart in the most direct manner (Fig. 2, *A*). In producing the tunnel and drawing the artery into it, we have adopted, with modifications, the method of Glenn and Beal.[2] To the ligature on the proximal end is tied the loop of a wire stylet. A traction suture may be placed in the myocardium just distal to the site of the proposed exit of the tunnel. A curved 13-gauge needle is inserted into the deep one-third of the myocardium from the apex toward the approaching internal mammary artery, emerging about 2.5 to 3 cm. away and avoiding all coronary branches (Fig. 2, *A*). If the ventricle is entered the needle should be withdrawn, cleansed, and reinserted. The stylet is inserted into the open end of the needle, and the needle, stylet, and artery are pulled through the myocardium simultaneously, avoiding angulation or torsion (Fig. 2, *B* and *C*). The needle is removed, leaving the artery, attached to the stylet, projecting about 1.5 cm. outside the heart. To avoid constriction, the entrance to the tunnel is enlarged with a scalpel and spread with a hemostat (Fig. 2, *C*). The

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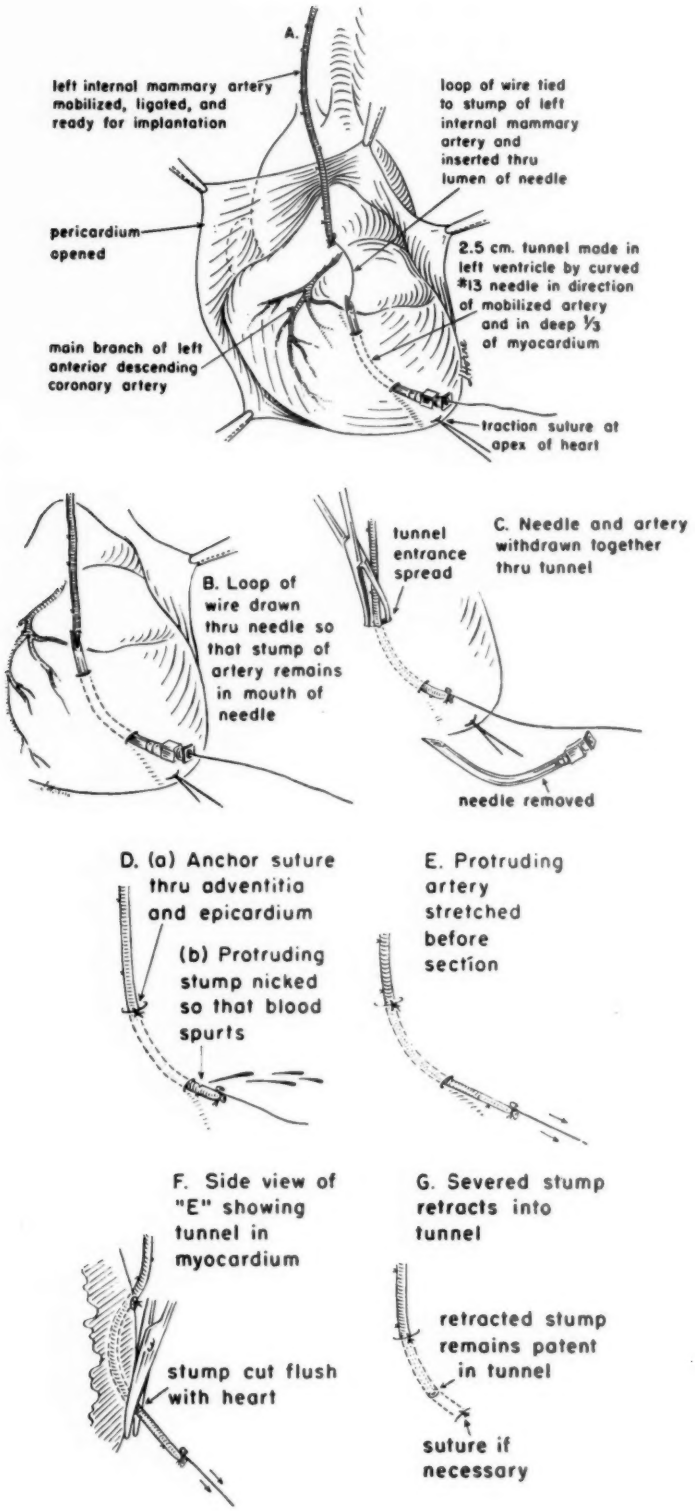
A.
left internal mammary artery mobilized, ligated, and ready for implantation
loop of wire tied to stump of left internal mammary artery and inserted thru lumen of needle
pericardium opened
2.5 cm. tunnel made in left ventricle by curved #13 needle in direction of mobilized artery and in deep 1/3 of myocardium
main branch of left anterior descending coronary artery
traction suture at apex of heart
B. Loop of wire drawn thru needle so that stump of artery remains in mouth of needle
tunnel entrance spread
C. Needle and artery withdrawn together thru tunnel
needle removed
D. (a) Anchor suture thru adventitia and epicardium
(b) Protruding stump nicked so that blood spurts
E. Protruding artery stretched before section
F. Side view of "E" showing tunnel in myocardium
stump cut flush with heart
G. Severed stump retracts into tunnel
retracted stump remains patent in tunnel
suture if necessary

Fig. 2.—Technique of implantation of artery.

artery is anchored to the tunnel entrance by a nonconstricting suture through its adventitia and the epicardium (Fig. 2, *D*), or better, by means of a ligated branch, if available. The protruding portion of the internal mammary artery is then nicked; a strong pulsatile flow of blood must come from the opening (Fig. 2, *D*). If not, the artery should be inspected and anything which interferes with free flow of blood should be corrected. After the patency of the implanted artery is proved, firm traction is made on it by means of the terminal ligature (Fig. 2, *E*), and the artery is cut flush with the epicardium (Fig. 2, *F*). It retracts at once into the tunnel (Fig. 2, *G*). Ordinarily there is no external bleeding. If a pulsatile flow comes from the tunnel, it indicates that the end of the implant is too close to the tunnel exit, and a suture may be necessary to close the tunnel exit and to control the bleeding. When the implant has been satisfactorily completed the pericardium is loosely approximated only if this produces no pressure of any kind on the implant. Additional incisions of the pericardium usually are necessary to avoid constriction of the implant as it enters the pericardial sac. If any doubt whatever exists as to whether the pericardium presses upon the implant or as to the possibility of future scarring around the implant, the pericardium should be left open.

The operation described may be performed quickly and easily with little risk. We have purposely omitted epicardial stripping and pericardial fat transplants[3] in this study. In 10 dogs, as soon as the implant was completed, depoheparin was given. Two of these dogs died of hemothorax and the administration of heparin was discontinued. In the heparin-treated dogs which survived, there was no improvement in the number of patent implants over those in the nonheparinized dogs.

SUMMARY

The technical aspects of implantation of the left internal mammary artery into the ventricular myocardium of normal dogs are described in detail.

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A SIMPLE APPARATUS FOR FREEZE-DRYING ARTERIES

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(From the Thoracic and General Surgical Services, Kennedy Division, Veterans Administration Hospital)

FREEZE-DRIED arterial homografts have been shown to be satisfactory for clinical use and there is little, if any, evidence that other types of grafts or prostheses are superior.[1-13] Some of the criticism of the method has been directed at the expense and the complicated technique required for the processing.

In discussing the management of freeze-drying apparatus with several groups involved in establishing a tissue bank, we have been impressed with the fact that the most frequent problems are due to attempted overrefinement of the technique. Changes in the absolute and relative values of temperature, pressure, and rate of diffusion produce significant changes in the tissue.[10] The detailed basic studies and large experimental series of freeze-dried grafts first done at the Naval Medical Research Institute[1, 5, 7, 9-12] used grafts processed at certain definite temperature and pressure levels. Before different levels of temperature and pressure are used, we believe one should be supported by a mass of experimental and clinical investigations at least as detailed as the original reports from Naval Medical Research Institute, notwithstanding one's infatuation with beautiful apparatus. Various studies have indicated that the elaborate techniques involving temperatures around –192° C. and pressures of 0.1 to 1 μ Hg are not as satisfactory for grafting purposes as the usual techniques.[5-7, 9-12] This difference in behavior is believed to be due to desirable changes in tissue protein resulting from the cruder techniques, with resultant loss of "antigenicity."[9] We have developed a simple, inexpensive, but very reliable machine which approximates the pressure-temperature curves of the original apparatus without difficulty.

A study of the equations* governing gases in a vacuum shows that the conductance is directly proportional to the fourth power of the diameter and

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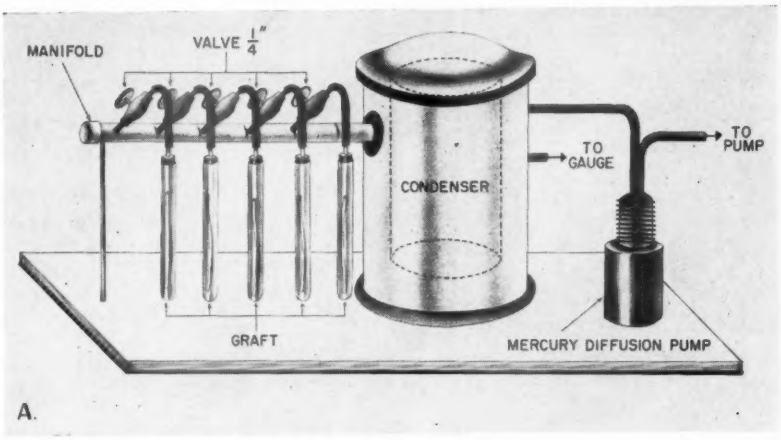
*Knudsen's equation, as given by Reimann[6] is:

$$C = \frac{\pi D^4}{128\eta l} + \frac{1}{W\sqrt{p}} \left(\frac{1 + \frac{\sqrt{p}\ D\ Pm}{\eta}}{1 + \frac{1{\cdot}24\ \sqrt{p}\ D\ Pm}{\eta}} \right)$$

C = conductance D = internal diameter of the pipe
l = length of the pipe η = viscosity p = density Pm = mean pressure
w is expressed by: $\frac{2\ \pi}{6}\ \frac{(1 + 4/3\ D)}{D^3}$ This is simplified to:

$$C = \frac{3.558 \times 10^5 D^4}{l} PM + \frac{1.44 \times 10^4 D^3}{l}$$ at a temperature of –10° C.

inversely proportional to the length of the connecting pipe. Therefore, for an efficient system, one should make the diameter as large as practical and the distance from the graft to the condensing surface as short as possible. This basic principle is all too frequently ignored. Examination of Fig. 1 illustrates the marked improvement in the length and diameter obtained in the new machine. Fig. 2 is a plan of the apparatus and Fig. 3 is a photograph of the completed machine.



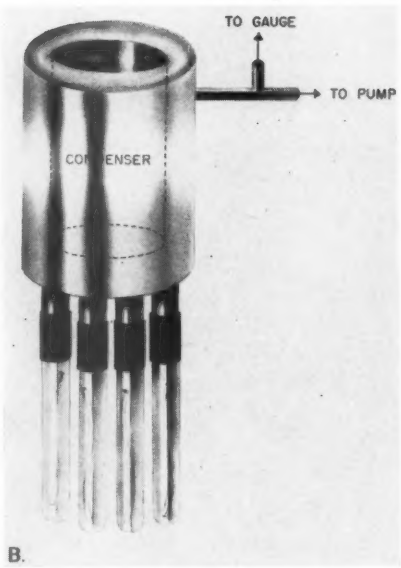


Fig. 1.—*A*, Schematic diagram of a commonly used type of installation. From the graft tube to the condenser is about 60 cm. and the internal diameter of the pipes and valve is about 0.6 cm. *B*, Schematic diagram of our installation. From the graft tube to the condenser is about 7 cm. and the internal diameter of the pipes is about 3 cm.

The relative conductance for apparatus *A* would be approximately 3.9×10^4 Gm./c.c. and for apparatus *B*, 2.4×10^8 Gm./c.c. at 50 μ Hg operating pressure.

A Flosdorf modification (Stokes Machine Company) of the McLeod gauge is used to measure pressure and is placed distal to the condenser to protect it from the ill effects of water vapor. The elaborate and expensive electrical

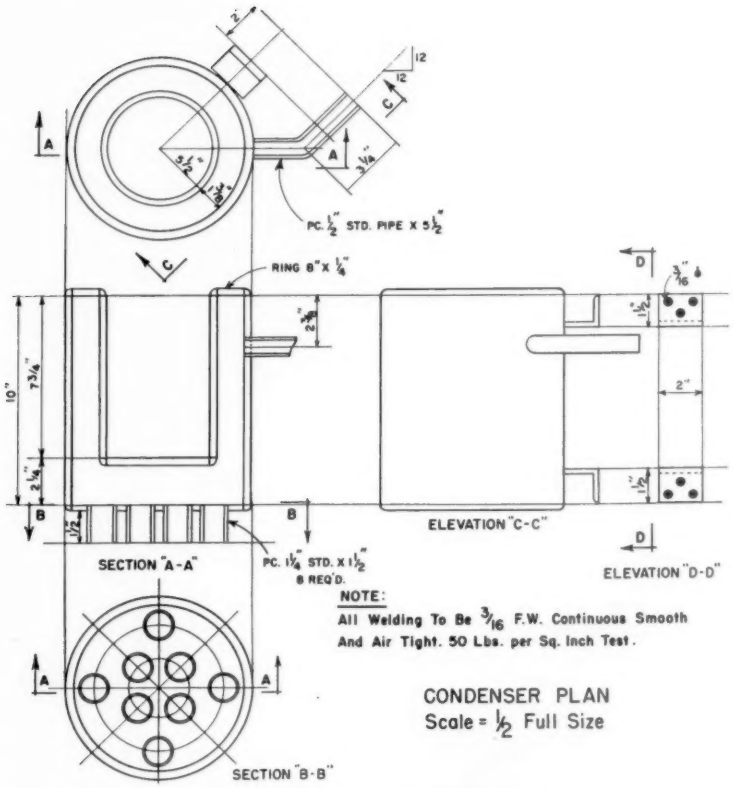

PC. ½" STD. PIPE X 5½"
RING 8" X ¼"
ELEVATION "C-C"
ELEVATION "D-D"
SECTION "A-A"
PC. 1¼" STD. X 1½" 8 REQ'D.
SECTION "B-B"
NOTE:
All Welding To Be 3/16 F.W. Continuous Smooth And Air Tight. 50 Lbs. per Sq. Inch Test.
CONDENSER PLAN
Scale = ½ Full Size

Fig. 2.—A working plan of the freeze-drying apparatus without its standard mechanical vacuum pump and gauge.

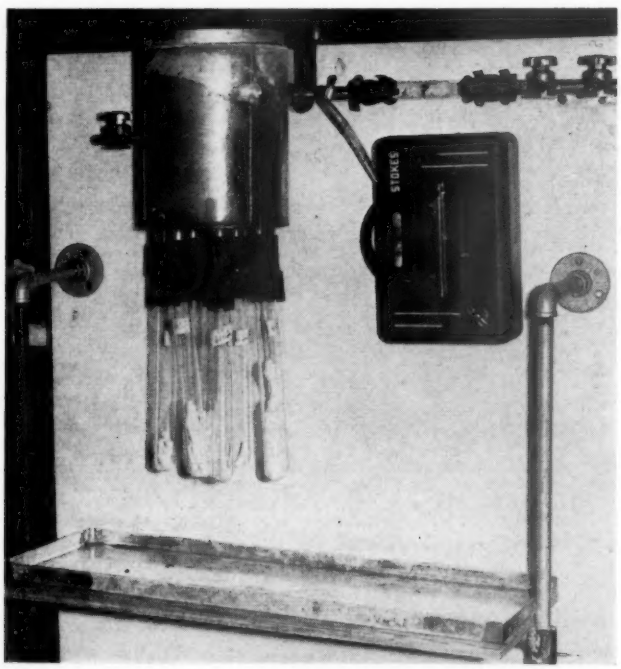


Fig. 3.—A photograph of the completed machine. The vacuum pump is on a shelf immediately behind the condenser.

ionization gauge and conductance gauge are not needed in such a system since, being secondary measuring devices, they must themselves be frequently calibrated against the McLeod gauge.

Mercury and oil diffusion pumps are not preferred because they obtain pressures below the recommended levels and are expensive and complicated to operate. A good standard mechanical vacuum pump is used.

The need for liquid nitrogen in the condenser is obviated by the simple expedient of keeping the tissue at –72° C. by dry ice until the ethylene oxide (or probably the ethylene oxide hexahydrate, $C_2H_4O_6H_2O$)[13] is removed at the operating pressure of 30 to 70 μ Hg. This usually takes only a few hours. This selective evaporation is possible because of the much higher vapor pressure of ethylene oxide than that of water at these temperatures.

In processing the grafts, fresh arterial segments are placed in sterile tubes and ethylene oxide placed over the segments for 30 minutes. The excess ethylene oxide is then poured off (under a hood) and the segments, in their tubes, are quick-frozen in dry ice-alcohol mixture (about –72° C.). The tubes are then attached to the machine. Dry ice is packed around the tubes and the pump is turned on. The only other maneuver needed during the process is to keep the condenser filled with dry ice and alcohol. The sublimation of the dry ice around the tubes and resulting slow warming keep the pressure within the desired limits with no difficulty. After 72 hours the grafts are sealed under a vacuum and stored on shelves at room temperatures.

Machines of this design have been used for 3 years at the Medical College of Alabama and for 2 years at the Veterans Administration Hospital, Memphis. Hundreds of grafts have been processed and successfully used in humans as well as animals. There have been no known graft failures which showed evidence of poor freeze-drying.

SUMMARY

A simple inexpensive apparatus* which satisfactorily processes freeze-dried arteries is described.

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CLINICAL EXPERIENCES WITH HEAT-SEALED DACRON GRAFTS

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DIRECT surgical attack on aneurysms, thrombo-occlusive diseases, and segmental arteriosclerotic occlusions in the aorta is an accepted surgical procedure. Replacement of excised aortic and arterial segments by grafts has proved to be much superior to endartectomy and aneurysmorrhaphy.[1, 4, 6] Homografts at first were thought to be an ideal substitute as a replacement material. However, serious structural destruction observed in thoracic and abdominal aortic replacements have been well documented and are cause for concern. Marked arteriosclerotic, calcific, and retrogressive changes have been reported. Dilatation and aneurysm formation which was once feared has become a reality.[3, 7, 12, 15]

The procurement of suitable homografts is often impossible and their preservation is a time-consuming and expensive proposition. There is, therefore, an urgent need for a suitable replacement graft. The use of synthetic fabrics such as Vinyon-N, Orlon, nylon, and Dacron has proved encouraging both experimentally and clinically.[2, 5, 8-11, 13, 14, 16, 19, 20] The availability, adaptability, durability, and ease of sterilization are decided advantages in favor of these fabrics. The ideal prosthetic material either has not been found or its potentials have not been fully realized despite the tremendous amount of experimentation.

Recently we have been experimenting with methods of improving and simplifying the construction of Dacron taffeta grafts. The material is similar to that studied by Deterling and Bhonslay[9] and reported as one of the most successful in their series. It has the advantage of low porosity, and the shrinkage is less than 2 per cent with autoclaving. The Dacron taffeta is woven from monofilament thread and has thread count of 116 per inch in the warp and 100 per inch in the filler.

Two fabrics, Vinyon-N and nylon, are available in sheets or as braided seamless tubes. The sheets are machine-sewed to predetermined widths, branching, and lengths. The bilateral stitching leaves a wide edge to avoid fraying and a cuff of approximately 1 cm. of the fabric is turned back at the ends for suturing. No satisfactory adjustments can be made in the length or width of these grafts. The turning of an additional cuff, if the replacement graft is too long, reduces the size of the lumen at the end and may cause wrinkling. If

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fashioned at the operating table and sterilized it is too time consuming. The 2-layer cuff is often difficult to stitch and may cause bending of the needle or tearing of the host vessel.

The braided seamless tubes are from 2 to 2½ times thicker than the sheets of cloth, and in our experience alarming blood loss through the fabric has been encountered frequently.

The method we selected for converting sheets of Dacron cloth into tubes by heat sealing the edges was similar to that described by Nanson.[17] Heat-sealing properties of these polymers have been well known. Such a property insures ready tailoring of a variety of tubular patterns at the operating table to meet the needs of the individual case. Straight tubes or bifurcation replacements can be made. In our hands, particularly clinically, there was less sweating from this material than from Vinyon-N and nylon fabrics.

Experimentally the heat-sealed fusion lines proved to be remarkably strong.[18] Dacron tubes were subjected to a progressive hydrostatic force. The force was measured by a column of mercury 1,800 mm. in height. Six of the 12 tubes failed to rupture at 1,800 mm. Hg. The average height at rupture was 1,717 mm. Hg. This was a safety factor of approximately 9 times that of a systolic pressure of 200 mm. Hg in dogs. The length of time that the tubes would withstand such pressures was not determined.

Twelve similar tubes were placed in the thoracic aorta in as many dogs. Eight dogs were sacrificed and 4 died from other causes; the longest survival was 180 days. All grafts were functioning normally and there were no clots at the seams or anastomoses. The grafts and adjacent proximal and distal aorta were subjected to increasing hydrostatic pressure. An average of 1,586 mm. Hg pressure was required before rupture of the graft or aorta occurred.

This experimental evidence indicated that heat-sealed Dacron taffeta tubes were remarkably strong. It appeared that they would be good substitutes for blood vessels. They are easily fashioned at the operating table and the length and width of the substitute graft can be tailored more accurately to conform to the host vessel and defect. A minimum of time is required and blood loss from the suture line and graft are negligible.[18]

Two patients with aortic aneurysm and 3 patients with thrombo-occlusive disease were operated upon. In each case the lesion involved the aortic bifurcation. Heat-sealed bifurcation Dacron grafts were used successfully to bridge the gap (Fig. 1).

CASE REPORTS

CASE 1.—J. O. H., a 66-year-old white man, was admitted to the hospital on Dec. 25, 1956. He had abdominal pain and vomiting. Diagnostic studies established the presence of kidney stones. He gave no history of an abdominal mass or of pain in his legs when walking. On physical examination his blood pressure was 210/110 and pulse rate was 90. A large, firm, pulsating mass was felt just to the left of the umbilicus. This mass was approximately 8 by 10 cm. in size. On Jan. 3, 1957, an aortogram was performed utilizing Urokon as a contrast medium. The dye was well visualized in the upper abdominal aorta. At approximately 2 cm. below the renal arteries, the abdominal aorta was noted to be somewhat dilated and irregular. The aorta deviated markedly to the left. No dye was seen in the femoral arteries.

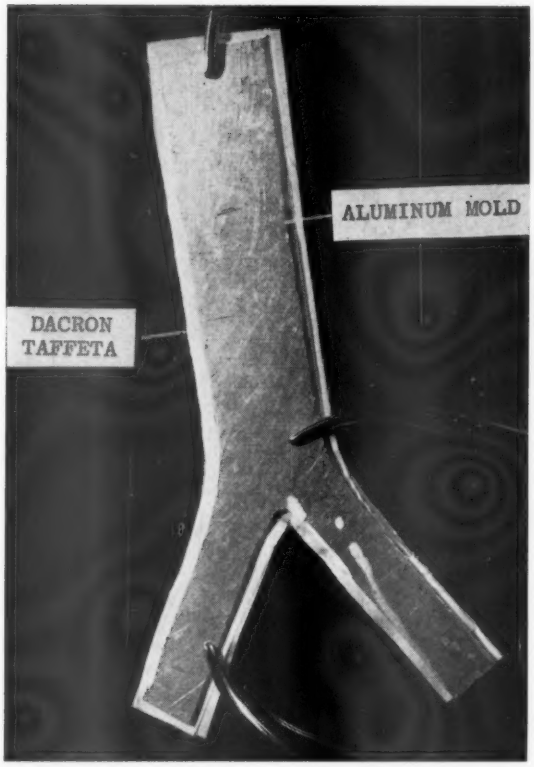

Fig. 1.—Illustration of aluminum mandril or templet used to fashion abdominal aortic graft with iliac bifurcation. Two sheets of Dacron are held between the 2 plates of the mandril by forceps. The heat seal is made by melting the 2 plastic sheets along the contour of the mandril. The graft is then cut to desired length and cuffs are turned for the anastomosis. The grafts are made under aseptic conditions at the operating table. The Dacron taffeta is kept sterile in flasks of cetylcide 1:1000 solution.

Fig. 2.—Heat-sealed Dacron bifurcation graft following resection of terminal aorta and proximal iliac arteries. The graft was fashioned at the operating table. Exact measurements were made. The proper sized mandril was selected. The Dacron taffeta was cut allowing 3 to 4 mm. for heat sealing under aseptic conditions and was heat sealed just outside the operating room with an alcohol lamp to prevent explosions.

On Feb. 14, 1957, an exploratory laparotomy was performed. A large aneurysm was found. It involved the distal two-thirds of the aorta, the bifurcation, and the proximal iliac arteries. The aneurysm was excised. A heat-sealed Dacron bifurcation graft was tailored to the length and width of the defect and grafted (Fig. 2).

Postoperatively the patient did well. Femoral pulsations and all peripheral pulsations of the lower extremities were present. On the seventh postoperative day the wound dehisced and was closed. There were no other postoperative complications. The patient was discharged from the hospital on March 12, 1957. After a 7-month follow-up period the patient's activities were normal. Excellent pulsations were present in the peripheral arteries of the lower legs.

CASE 2.—R. O. C., a 67-year-old white man, was admitted to the hospital Feb. 22, 1957. He had complained of abdominal pain of one week's duration. The diagnosis of an abdominal aortic aneurysm had been made in November, 1955, during an exploratory laparotomy and appendectomy. An aortogram made 2 months later showed good filling of the proximal abdominal aorta, but no filling beyond this point. There was excellent collateral circulation.

On examination the blood pressure was 150/100 and pulse rate was 78. A mass was felt in the mid-abdomen which extended toward the left. The mass was approximately 8 by 7 cm. in diameter. It was firm and pulsated.

On Feb. 28, 1957, an exploratory laparotomy was performed. A large fusiform aneurysm was found. The distal two-thirds of the abdominal aorta and bifurcation was involved. The aneurysm was excised. A heat-sealed bifurcation Dacron graft was tailored to the length and width of the defect and anastomosed.

Postoperatively the patient had an uneventful recovery. Femoral pulsations and all peripheral pulsations of the lower extremities were present. After a 7-month follow-up the patient's activities were normal and excellent pulsations were present in the peripheral arteries of the lower legs.

CASE 3.—C. E. L., a 59-year-old white man, was admitted to the hospital on Feb. 25, 1957. He complained of pains in both lower legs while walking during the past 4 years. The pain was relieved by rest. During that period the pain and cramps had become progressively worse and at the time of admission to the hospital the patient was only able to walk one block without resting. There had been no change in color of his lower extremities; however, he had noticed that they were colder than usual. He had also developed pain in the right hip which was of one year's duration. In the past 6 or 7 months there had been loss of libido and he had developed impotence.

On physical examination the blood pressure was 140/90 and pulse rate was 88. There was good color of both lower extremities and the temperature of both lower legs was normal. The femoral arteries were palpable, but definitely weak. Pulsations in the dorsalis pedis and anterior tibial arteries were perceptible. On March 4, 1957, an aortogram was performed utilizing Urokon as a contrast medium. The dye was well visualized in the aorta. The proximal aorta was essentially normal. The lumen of the abdominal aorta appeared smaller at the third lumbar vertebra and at its bifurcation it was partially occluded. The right common iliac artery was not visualized. There was notching of the lumen of the proximal left common iliac artery at its junction with the aorta.

On March 8, 1957, an exploratory laparotomy was performed. The diagnosis of thrombo-occlusive disease was confirmed. The lower one-third of the abdominal aorta and the proximal 3 cm. of the iliac arteries were excised. A heat-sealed Dacron bifurcation graft was tailored to the length and width of the defect and anastomosed.

Postoperatively the patient did well. Femoral pulsations and all peripheral pulsations of the lower extremities were present. Oscillometric tracings were normal. The patient was discharged on the tenth postoperative day. After 6 months his activities were normal. He had experienced no pain in his hips or legs since hospitalization. Excellent pulsations were present in the peripheral arteries of the lower legs.

CASE 4.—J. B., a 48-year-old white man, was admitted to the hospital on July 18, 1957. He had complained of pain in both hips and lower extremities when walking during the

past 6 years. For approximately 4 years he had noticed pain in both hips on walking. The pain in both hips and the lower legs had increased in severity, and at the time of hospital admission he was able only to walk one block without resting. This patient had noticed impotence for one year. Two months prior to this admission he had undergone resection of the distal abdominal aorta and proximal 2 cm. of the iliac vessels because of thrombo-occlusive disease of this segment. Organized blood clots had been removed from the distal ends of both common iliac arteries. An Edwards crimped nylon graft had been employed. Following this surgical procedure no pulsations were felt in the femoral arteries or in the peripheral vessels of the lower legs. Oscillometric studies showed only faint pulsations in both lower extremities. After discharge the patient continued to complain of pain in both lower extremities and to a minimal degree in the hips. A skin resistance test was done and was interpreted as decreased sweating in both legs with less than normal increase in temperature after diathermy.

On physical examination there was a blood pressure of 200/100 and a pulse rate of 80. The blood pressure could not be obtained in either lower extremity. Both lower extremities were pale; there were no peripheral pulsations felt. On July 19, 1957, an aortogram was again performed. Contrast medium outlined a normal aorta above the renal arteries, but no dye could be seen beyond these vessels. There was extensive collateral circulation and dye appeared in the left common iliac artery through retrograde flow. The right common iliac artery was not visualized by the dye.

On July 22, 1957, an exploratory laparotomy was performed. The abdominal aorta was completely occluded from the level of the renal arteries down to and including both common iliac arteries. The right hypogastric artery was also occluded. The Edwards crimped nylon graft was solid and contained an organized clot. The abdominal aorta was excised approximately 2 cm. below the renal arteries and a fresh clot was removed from the proximal lumen. The right common iliac artery was transected approximately 2 cm. distal to the hypogastric artery and the left common iliac artery was transected approximately 1 cm. proximal to the left hypogastric. A heat-sealed Dacron graft was tailored to the length and width of the defect and anastomosed.

Postoperatively the patient developed a paralytic ileus and an abdominal abscess. The pulsation of the femoral arteries and peripheral vessels remained good. On the tenth postoperative day there was a sudden hemorrhage from the site of exploration of the right femoral artery in the thigh. The suture line was reapproximated. The patient recovered from the complications and was discharged on Aug. 31, 1957.

CASE 5.—M. C., a 39-year-old Puerto Rican, was admitted to the hospital on July 25, 1957. He complained of pain in the calf of the right leg while walking during the previous 9 months. During the 5 months prior to admission to the hospital the pains had become progressively worse and at the time of admission he was able only to walk 1½ blocks without resting. There had been no color change of his lower extremities; however, he had noticed that his right leg was colder than usual. He had no hip pain. In April, 1957, an aortogram had been done elsewhere. The diagnosis of thrombo-occlusive disease of the abdominal aorta and iliac arteries was established.

On physical examination the blood pressure was 118/74 and pulse rate was 78. The abdominal aorta pulsated well. The right femoral artery was barely perceptible. The left femoral artery was weaker than normal. There were no pulsations noticed in either lower extremity. The right foot was noted to be colder than the left.

On Aug. 9, 1957, an aortogram was performed utilizing Urokon as a contrast medium. The dye was well visualized in the proximal abdominal aorta. The distal one-third of the abdominal aorta was narrowed and the right iliac artery was totally blocked at the bifurcation of the abdominal aorta. There was considerable notching of the left iliac artery. Both hypogastric arteries were visualized through collateral circulation.

On Aug. 15, 1957, an exploratory laparotomy was performed. The diagnosis of thrombo-occlusive disease was confirmed. The abdominal aorta was transected just below

the inferior mesenteric artery. The iliac arteries were divided approximately 1 cm. above the hypogastric arteries on the right and 3 cm. on the left. A heat-sealed Dacron bifurcation graft was tailored to the length and width of the defect and anastomosed.

Postoperatively the patient did well. Femoral pulsations were present bilaterally, but the pulsation of the left femoral was weaker than that of the right. Oscillometric tracings were essentially normal.

DISCUSSION

Dacron taffeta grafts, tailored at the operating table and sealed by heat, have been used in 5 patients. In each case a bifurcation graft was required.

Heparin solution of minimal dosage was instilled into the proximal aorta and iliac arteries following cross-clamping of the vessels. Sweating or hemorrhage of the graft was minimal following release of the cross-clamps. In 2 cases the sealed edges required a stitch or two where a clamp had been placed on the graft. There has been no appreciable bleeding from the suture line.

Anticoagulant therapy was employed in only one case. However, it was discontinued on the third postoperative day when the patient developed signs of internal hemorrhage. Protamine and rapid whole blood transfusions were given which controlled the hemorrhage and it was not necessary to explore the wound. The patient later developed an abdominal abscess. Drainage and antibiotics effected a cure.

In this case a Dacron heat-sealed graft was used to replace a woven seamless nylon graft. The nylon graft had evidently clotted soon after the previous operation.

Our clinical experience with bifurcation grafts before the introduction of the heat-sealed bifurcation Dacron grafts consists of 24 cases. There were 11 homologous, 5 nylon, 4 Orlon, and 3 Dacron grafts. All but 2 of the fabric grafts were of the bilateral seam type. Woven seamless nylon fabrics were used in 2 cases. A homologous graft clotted on the sixth postoperative day. One seamed nylon graft clotted 24 hours after insertion. Three grafts clotted before the abdomen was closed and required exploration through the host vessel. One was a woven seamless nylon graft and the others were of nylon and Orlon fabric with seams. Sweating of all of the replacement fabrics in this series was a discouraging feature.

Difficulty was encountered with adjustment of the prepared fabric. The length of the prepared fabric grafts required adjustment in all cases. Wrinkling occurred in all grafts in which the host lumen was larger than that of the fabric graft.

In 2 cases an abdominal abscess occurred. A homologous in one case and a nylon bilateral seam graft in the other had been used. In both instances the patients were readmitted because of infection and secondary hemorrhage. Both patients died.

In 2 cases the follow-up after replacement of an aortic bifurcation with a heat-sealed Dacron graft has been 7 months. There were no complications except in one patient. In Case 4 there was postoperative abdominal bleeding and the development of an abdominal abscess. However, the patient recovered.

Deterling and Bhonslay[9] reported on the heat-sealing method of preparing grafts. This method was proved satisfactory in animal aortic replacement. However, at the time of the report they had not implanted such grafts in humans since they believed the heat-sealed edge to be unreliable. Our experiences indicate that this is a safe method.

SUMMARY

1. Heat-sealed Dacron replacement grafts were used in 5 patients with excellent results. The cases are described and discussed.

2. Experimental testing of the strength of the heat-sealed union previously reported is reviewed. This method had established the safety of such a technique and so was put to clinical trial.

3. The principal advantage of the heat-sealed Dacron taffeta graft is that it can be tailored at the operating table to meet the needs of each individual case.

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INTERMITTENT POSITIVE PRESSURE BREATHING (IPPB/I) FOR THE PREVENTION AND MANAGEMENT OF POSTOPERATIVE PULMONARY COMPLICATIONS

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THE use of intermittent positive pressure therapy (IPPB/I) for the prevention and treatment of postoperative pulmonary complications has been gaining steadily in various hospitals throughout the country and abroad, although very little on the subject has appeared in the literature. Its use in the Buffalo General Hospital has increased steadily over the past 4 years and there are now 18 machines in almost constant service for medical and surgical patients. Intermittent positive pressure therapy for surgical patients is routine on some services and to date over 350 cases have been treated in this manner, with enthusiastic results and no serious complications. It is felt that this important adjunct to the postoperative management of surgical patients should be more widely known and understood.

In spite of the many advances in the care of the surgical patient, pulmonary complications continue to exist as major problems. Hypoxia, acidosis, hypercarbia, depression of the respiratory center, edema of the pulmonary membranes, trauma from intubation and suction tubes, transient periods of shock, reduction in the movement of the diaphragm, reflex neurogenic effects from abdominal visceral trauma, incorrectly placed abdominal bandages, and the well-known depressive effects of narcotics still have their deleterious effects even under the most carefully controlled circumstances. They have been minimized by the tremendous improvements in the modern care of the surgical patient but still exist, particularly in those patients with pre-existing pulmonary changes, such as emphysema, pulmonary fibrosis, chronic bronchitis, and bronchiectasis.

The approach to these problems involves improved anesthetic and surgical technique, the judicious use of pre- and postoperative medications, the treatment of pre-existing pulmonary conditions, correct timing for surgery, careful handling of the patient in the recovery room, and a long list of other well-studied considerations.

As important, however, as any of these phases is consideration for the ventilation in the postoperative patient. There has been traditional reliance upon

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good nursing care for the maintenance of ventilation, coughing, change in position, and the entire "stir-up" program in the postoperative period. With the steady decrease in the ratio of these nurses, a gradual default in this most important phase of surgical care has developed. This is particularly true for the patient after he has left the recovery room.

The use of mechanical intermittent positive pressure breathing (IPPB/I) has become a valuable adjunt to the prevention and management of postoperative pulmonary problems. It does not replace any of the many other necessary measures in the surgical patient but is a tremendous boost in painlessly maintaining adequate ventilation and the "pulmonary toilet," particularly in the patient who needs it the most.

The apparatus provides a controlled flow of gas, oxygen, or compressed air from a commercial cylinder or wall outlet to the patient using a mask or, more frequently, a simple mouthpiece. There are several commercial devices to accomplish this satisfactorily. We have used the Pulmonary Ventilator.*

The machine is controlled voluntarily and without effort by the patient's own respirations. When he starts to inhale there is induced an increased flow of gas into his lungs at a relatively low preset pressure, usually 15 to 20 cm. H_2O. When the pressure in his pulmonary system reaches this level, the flow of gas is automatically shut off, and the patient exhales comfortably without resistance at ambient or room air pressure. No further action occurs until he initiates his next inspiration and the cycle is repeated.

Construction is such that an aerosol spray can be and usually is incorporated in the gas flow, which has advantages from a therapeutic standpoint. This allows the administration of any chosen aerosol medication depending upon the pulmonary status of the patient. This is particularly advantageous in patients with chronic lung disease, emphysema, bronchitis, bronchiectasis, asthma, and so forth, in whom the incidence of postoperative pulmonary complications is generally the highest. It is also helpful in loosening tenacious postanesthetic secretions.

In essence, the use of intermittent positive pressure with aerosol aims *preoperatively* (1) to improve ventilation in altered lung tissue, (emphysema, and so forth), (2) to improve the "bronchial toilet," particularly in the patient with excessive secretions (bronchitis, bronchiectasis, and so forth), (3) to provide medications as indicated for bronchospasm and pulmonary infections, (4) to improve gas exchange in the anoxic or hypercarbic patient, and (5) to improve familiarity with the apparatus for the patient who will use it at routine intervals following surgery.

Postoperatively intermittent positive pressure breathing with aerosol aims (1) to provide adequate ventilation, at least periodically for the prevention of atalectasis, (2) to facilitate and increase removal of bronchial secretions, and (3) to provide medical therapy for bronchospasm, infection, anoxia, and even mild degrees of bronchial obstruction. The use of the machine has the advantage of achieving these results with very little patient effort and without crucially depending upon the individual administering the treatment. This is of considerable practical importance today.

*Mine Safety Appliances Company, Pittsburgh, Pa.

The general procedure is to introduce the patient to the apparatus by having it at the bedside for the several days prior to surgery. He is advised to use it himself with the proper aerosol medications every 4 hours during the day. This early introduction is of considerable psychologic advantage in addition to its therapeutic value. During this period the patient is able to give rather undivided attention to an understanding of the mechanics and principles involved. He learns to realize that what appears to be a complicated apparatus is really quite simple and relatively harmless. He can practice with it until he finds the most comfortable timing, pressure, and rate of air flow. He also has a chance to experience some of the minor operational disturbances which are inherent in the use of any mechanical apparatus but which do not disturb him as much as they would in the immediate postoperative period. In fact, the patient trained in this way frequently can explain how and when the machine is used to his changing shifts of nurses.

Postoperatively the orders are for 10 to 20 mechanically assisted ventilations every hour for the first 24-hour period and then every 2 to 4 hours thereafter, depending upon the condition of the patient. It is not necessary to tire the patient to achieve adequate periodic ventilation. In many cases he is able to administer this to himself just as he did preoperatively. If not, there has been little difficulty in getting the nurses to do this at the proper intervals. For some reason they have more respect for an order to administer a mechanical treatment such as this than they do for the responsibility and effort to "cough the patient" periodically.

One of the immediate consequences of these assisted ventilations is to shift the position of secretions in the bronchial tree which automatically initiates a cough reflex. This usually occurs within 15 minutes after treatment and the patient has no alternative but to cough. However, he has already learned or been advised of this before surgery, particularly that this is a desirable effect and is not dangerous if the wound is properly supported. In contrast to the exasperating efforts of trying to get some postoperative patients to cough voluntarily this is quite simple and usually more effective.

The long-feared concern that intermittent positive pressure breathing would impound bronchial secretions instead of loosening them has not been substantiated. In fact, with the addition of detergents and bronchodilators the opposite has been the case, sometimes dramatically so. This is particularly true in those individuals with underlying pulmonary disease in which the value of this as medical therapy has been well demonstrated.

A tracheostomy adapter is available for some of the IPPB/I machines and the program can be continued with no essential change in the tracheostomized patient. Other usual therapeutic measures are not altered or disturbed by using a program of IPPB/I.

It is important to emphasize that these postoperative treatments are best given with compressed air instead of oxygen. It is also important to emphasize that while the increased intrathoracic pressure with this type machine is of short duration (Fig. 1) it can be deleterious if the patient is in any degree of shock. The use of IPPB/I is contraindicated in such circumstances.

Several representative case reports will illustrate the application and use of intermittent positive pressure breathing in the surgical patient.

CASE REPORTS

CASE 1.—A. A. was a 64-year-old white housewife who had multiple hospital admissions since 1926. She had chronic bronchial disease of many years' duration and produced as much as one-half to one cupful of sputum a day. In 1954 a colectomy and double-barreled colostomy were performed for a perforated diverticulum. Postoperatively she experienced evisceration as a result of a chronic productive cough, leaving a large incisional hernia as a result. In 1955 she was readmitted for closure of the colostomy and repair of her ventral hernia. Her productive cough continued.

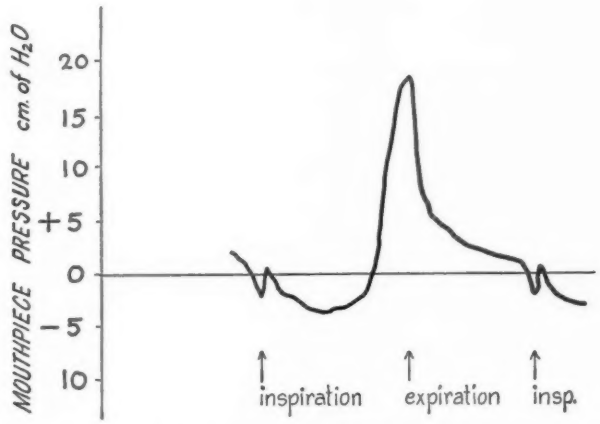


Fig. 1.—Diagram of the pressure curve produced at the mouthpiece by the Pulmonary Ventilator, IPPB/I. The length of this respiration is variable and is determined by the patient's voluntary rate of breathing. The apparent negative pressure is a Venturi effect from rapid inflow of air.

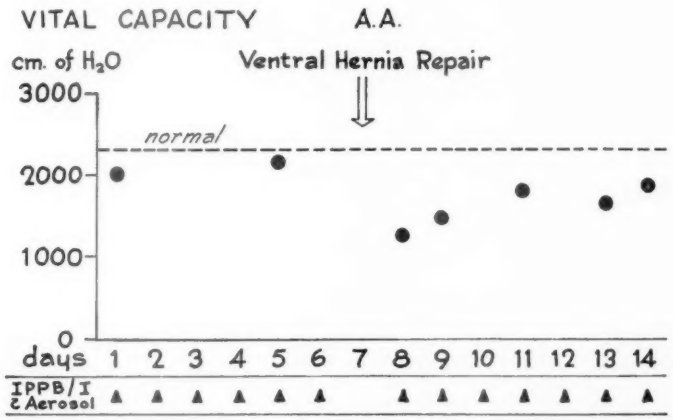


Fig. 2.—The pre- and postoperative vital capacities of a patient with chronic bronchial disease treated with intermittent positive pressure breathing (IPPB/I). There were no pulmonary complications.

Preoperative evaluation of her pulmonary status by the anesthetists leads them to believe that major abdominal surgery was too great a risk at this time. Intermittent positive pressure therapy with aerosol medication was added to her preoperative regime with marked improvement in her pulmonary status. She withstood the surgical procedure well and on continued IPPB/I therapy convalesced without complication though her vital capacity was significantly reduced (Fig. 2). The maximum rectal temperature elevation in the entire postoperative period was 100° F. There were no complications.

In 1956 she was readmitted, this time for surgical removal of a carcinoma of the stomach. She was again treated for 6 days preoperatively with IPPB/I, in addition to the usual preoperative routine. She withstood a subtotal gastric resection without complication and there was no evidence of atelectasis. Her temperature was minimal in the face of chronic bronchial disease.

CASE 2.—M. M., a 64-year-old white housewife, was admitted with the chief complaint of "soreness in the pit of her stomach" for one year. She had a 15-year history of pernicious anemia for which she had been under constant supervision and therapy. She was placed on IPPB/I therapy 2 days before surgery and continued afterward for 6 days. A total gastrectomy and splenectomy (thoracoabdominal approach) was performed for carcinoma of the stomach.

On the first postoperative day there were moist rales, rhonchi, and wheezes diffusely throughout her chest. Her vital capacity decreased by over 50 per cent, but these cleared satisfactorily by the end of that day, and it was felt a major pulmonary complication was averted. Though her vital capacity remained low her postoperative course was uneventful. (Fig. 3.)

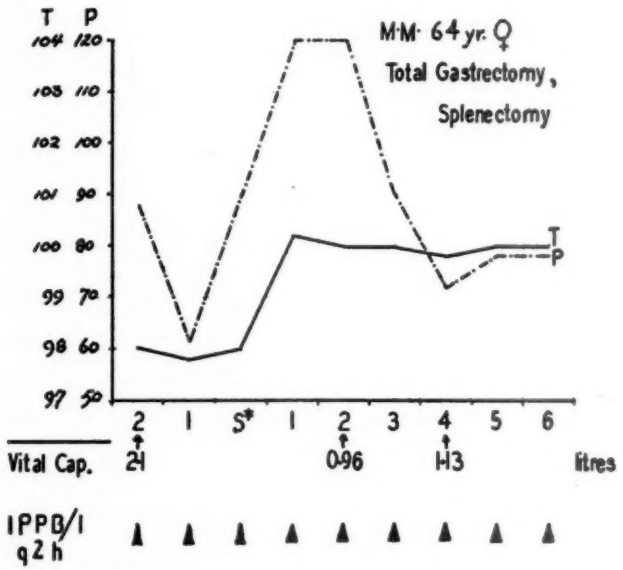


Fig. 3.—The pre- and postoperative course of a 64-year-old woman who had a total gastrectomy and splenectomy through a thoracoabdominal approach. Intermittent positive pressure therapy (IPPB/I) was used and no evidence of pulmonary complications developed in spite of the markedly reduced vital capacity.

CASE 3.—This third case, with a fatal outcome, is presented as a demonstration of the efficacy of this management of pulmonary problems under extreme conditions. H. B., a 43-year-old married white laborer, was admitted during the night with an acute abdominal crisis of several hours' duration. He was taken to surgery immediately, where a huge 4 cm. ruptured duodenal ulcer was repaired. His postoperative course was stormy throughout, with distention, vomiting, and the other complications of peritonitis. With the periodic use of IPPB/I, quantities of thick and bloody tenacious sputum were brought up. He would not cough satisfactorily in the intervals between treatment.

He died on the sixth hospital day of advanced peritonitis. At post-mortem examination, however, his lungs showed minimal congestion but were otherwise clear.

This was considered a demonstration of the effectiveness of IPPB/I therapy in maintaining the integrity of the pulmonary system under extreme circumstances. This case

also illustrates that IPPB/I can be of value even if employed after trouble has started. However, it is not nearly as satisfactory or as frequently effective as when the patient has adjusted himself to the program before surgery.

DISCUSSION

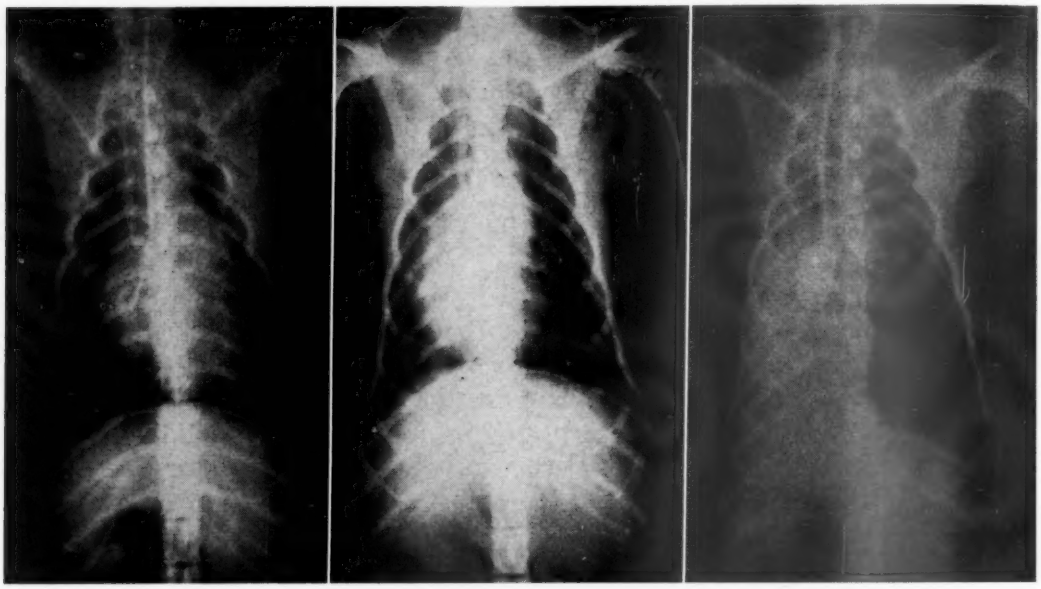
Postoperative pulmonary complications have been somewhat neglected in the American literature of late. It might be assumed that their significance and incidence had been accordingly reduced, but clinical experience does not support this assumption. Postoperative pulmonary complications are still a major problem particularly following upper abdominal surgery in men more frequently than in women, in the obese, in smokers, and in patients with acute or chronic respiratory infections. The incidence also increases with age and the length of surgical procedures.

As recently as 1954 Thoren[11] found pulmonary changes in 41.9 per cent of a carefully studied group of patients who had gall-bladder surgery. These patients had all the advantages of modern medical adjuvants. The incidence was reduced to 12 per cent by the addition of physiotherapy methods similar to the IPPB/I program to improve ventilation.

Other studies have found pulmonary complications in 30[10] and 34 per cent[5, 7] of all upper abdominal operations, and in 16 per cent[6] of inguinal herniorrhaphies. Kurzweg[4] summarizes the incidence of postoperative pulmonary complications as averaging 2.5 to 3 per cent of all operations, 10 to 20 per cent in abdominal surgery, and 20 to 30 per cent in upper abdominal surgery. Many of these are unsuspected until specifically sought by careful clinical and x-ray studies. Without these, the postoperative changes are often accepted as the natural sequelae of surgical procedures and not related to the pulmonary system.

That such complications continue to plague in spite of improved surgical and anesthetic techniques is not so surprising when one realizes that the basic anlage for such disturbances continue to exist unless specifically sought out and corrected. Preoperative bronchitis from smoking and of the many other causes is present in 40 per cent of men and 21 per cent of women as judged by the preoperative cough test of Greene and Berkowitz,[3] with all that implies for trouble after surgery. Postoperative vital capacity continues to be reduced as much as 60 per cent in our cases of upper abdominal surgery which is no improvement over similar measurements by Beecher in 1933.[1] He and others[2, 8] have demonstrated that changes in vital capacity are directly proportional to the pulmonary complication risk. That the decrease in vital capacity is not readily perceived clinically is understandable when it is realized that the minute volume ventilation, as measured by nitrogen wash-out methods, shows no such reductions.[11] Thus oxygenation can be maintained in spite of inactivity in a significant portion of the bellows mechanism. It is this bellows effect however which maintains the "bronchial toilet" to prevent the pulmonary complications. Shields[9] demonstrated in animals that intravenously injected organisms will selectively localize in any segment of the lungs, however small, in which there is bronchial obstruction or ventilation is interrupted. The anlage then for postoperative pneumonitis and atelectasis continues to present itself in any segment which is not ventilated.

The "bronchial toilet" is further interferred with by the well-known increased amount and viscosity of sputum following inhalation anesthesia, the depressed ciliary activity, and the associated bronchospasm. The decreased willingness and ability of the patient to cough together with the impaired cough reflex, particularly in patients with an abdominal wound, is well known. In addition it has recently been shown in animals that anesthesia alone will increase pulmonary congestion and decrease compliance in the pulmonary bed. This can be relieved by periodic "flushing" of the lungs with mild pressure, which the average postoperative patient may or may not do.



A. *B.* *C.*

Fig. 4.—The effect of right bronchial occlusion in the dog while breathing room air as compared with 100 per cent oxygen. Note shift of heart shadow with increasing atelectasis. *A*, Control. Bronchial balloon in position in the right main stem bronchus. *B*, Partial atelectasis several hours after occlusion while breathing room air. *C*, Complete atelectasis 15 minutes after occlusion while breathing 100 per cent oxygen.

It is generally assumed that this "flushing" procedure is accomplished by the anesthetist at the end of the surgical procedure. However, this is generally done with a high percentage of oxygen which has its own hazards. This is demonstrated in Fig. 4, the roentgenograms of dog lungs before and after bronchial occlusion while breathing 100 per cent oxygen as compared with room air. Complete atelectasis of the occluded side appears within 15 minutes from the rapid and complete absorption of 100 per cent oxygen. If the animal is breathing air instead of 100 per cent oxygen, the collapse develops over a period of several hours since the 80 per cent nitrogen is not so readily absorbed. A postoperative patient who has been "washed out" with 100 per cent oxygen is an open invitation for rapid atelectasis and pneumonia if any material such as mucus is available for occlusion.

The increasing use of intermittent positive pressure over a period of several years in this and other hospitals in the management of surgical patients

has demonstrated clinically the value of this approach in the management and prevention of pulmonary complications. Carefully controlled evaluation is necessary to determine the statistical validity of this clinical impression. However, an adequately controlled analysis must include the variables of surgeon, anesthetist, the individual patient, length and type of surgery, anesthetic agent, medications, the amount and type of nursing care, and the many other factors which enter into this problem. Most suggestions for the improvement of postoperative management of patients have demonstrated improvement in results, and the common denominator to each of these appears to be closer attention to the patient postoperatively. This factor alone will often be sufficient without any of the additions, mechanical or otherwise. Perhaps the success with IPPB/I has been on the same basis. Physiologically, however, it has substantial grounds for its support and, if, in addition, it is a means of focusing attention on the postoperative importance of adequate ventilation the improvement in results is quite acceptable.

We have not seen a surgical patient to whom any harm was done by the application of this procedure when used properly. It appears to be a major contribution in the prevention and treatment of postoperative pulmonary complications.

SUMMARY

1. Postoperative pulmonary complications continue to be a significant problem, particularly in patients with underlying disease of the lungs or bronchi for whom major abdominal surgery is indicated.

2. Mechanical intermittent positive pressure breathing has been used successfully over a period of several years to improve the postoperative ventilation, to increase the efficiency of the "bronchial toilet," and to control the effects of underlying disease in producing such complications.

3. The clinical impression is that this is a major contribution in the prevention and treatment of postoperative pulmonary complications.

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RUPTURE OF AORTIC ANEURYSMS INTO GASTROINTESTINAL TRACT

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ON RARE occasions, aortic aneurysms may rupture into the gastrointestinal tract, giving rise to massive bleeding. Rapid exsanguination from this catastrophe is unusual; however, in most instances there is sufficient time between the onset of bleeding and death to allow surgical intervention. In those patients previously reported with this condition, the diagnosis was rarely suspected prior to autopsy. This usual failure to diagnose or to strongly suspect the condition prior to autopsy, together with the comparative recentness of the development of the surgical techniques required to cope with the problems involved, explains our inability to find any report of such occurrence being treated surgically.

Our recent experience with a patient having an abdominal aneurysm which had ruptured into the duodenum in whom the correct diagnosis was made on admission and in whom surgical treatment was carried out prompts this report.

CASE REPORT

R. M., a 61-year-old white man, was admitted to the Eugene Talmadge Memorial Hospital on Oct. 25, 1956, because of hematemesis of approximately 500 c.c., 8 hours prior to admission, associated with abdominal pain, minimal nausea, and syncope. He had been given intravenous fluids and 500 c.c. of whole blood at a local hospital before transfer here. Throbbing, right midabdominal pain without radiation had been present intermittently for the preceding 5 to 6 years, had become progressively worse in the preceding 6 months, and had been severe and constant for the past 3 days. Pain was unassociated with food ingestion but was somewhat relieved by baking soda. It had been accentuated recently by coughing, defecating, or straining. He denied previous hematemesis, hemoptysis, and melena, but during the preceding 10 months anorexia had been progressive and he had lost 70 pounds.

The patient had been a known diabetic for 4 years; adequate control had been maintained by diet. He had been told 4 years previously that he had "gall-bladder trouble" and one year later that he had a duodenal ulcer; no surgery had been performed. A cerebrovascular accident had occurred 5 years previously, but recovery had been complete. He denied venereal disease, but admitted excessive ingestion of alcohol for many years as a young man.

The patient was well developed, poorly nourished, in no acute distress, but quite restless and apprehensive. Temperature 37.0° C., pulse 100, respiration 20, blood pressure 100/70. Examination revealed an 8 cm. in diameter, moderately tender, nonmobile, pulsatile mass in the right paraumbilical region and minimal enlargement of the liver, the edge of which was smooth and nontender 3 cm. below the right costal margin. All peripheral pulses were normal, and feces were of normal color and consistency. Laboratory data: hemoglobin 13.5 Gm. per 100 c.c., hematocrit 30, white blood count 7,500 per c.mm. with a normal differential count. Urinalysis was normal.

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Emergency upper gastrointestinal barium studies were attempted somewhat unsuccessfully due to the patient's refusal to cooperate, but no esophageal varices were identified. Although no further bleeding had occurred, immediate laparotomy was advised. The patient refused at first but several hours later agreed to surgery, which was begun about 8 hours after admission. The stomach and proximal duodenum revealed no evidence of disease; the distal duodenum and proximal foot of jejunum were about twice normal size and slightly reddened, an appearance thought to be compatible with very recent distention of considerable degree. This area blended gradually into normal jejunum. The large and small bowel were filled with old dark blood. Arising just distal to the origin of the renal arteries there was an aortic aneurysm measuring 10 by 6 by 6 cm. and extending to involve the proximal 2 to 3 cm. of each common iliac artery. There was no evidence of rupture except 2 small purplish spots encountered retroperitoneally as the third portion of the duodenum was being separated from the aneurysm. After the aorta distal to the renal arteries and each iliac artery was clamped, further dissection in this area disclosed considerable fibrotic reaction within which a very short fistulous tract 6 mm. in diameter was encountered connecting the anterosuperior aspect of the aneurysm with the lumen of the third part of the duodenum (Fig. 1). The opening was occluded by fresh thrombus at its aneurysmal orifice. A 2 cm. in diameter excavation into the body of the fourth lumbar vertebra was present posteriorly.

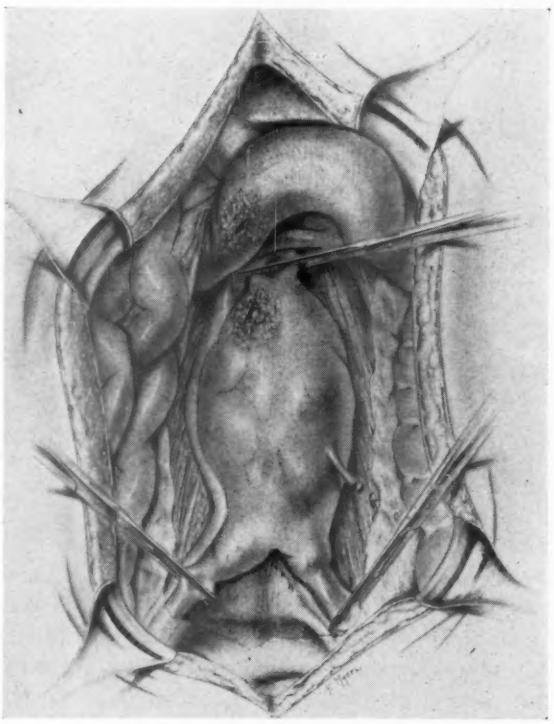

Fig. 1.—Artist's drawing of photograph taken at operation showing the aneurysm in situ. The duodenum has been dissected free from the aneurysm and rotated superiorly.

The aneurysm was resected, leaving only that portion of the right lateral wall intimately adherent to the inferior vena cava, and vascular continuity was restored by the insertion of a previously prepared Y-shaped combination Ivalon and Teflon graft (Figs. 2 and 3). The opening in the duodenum was closed.

Cultures from the interior of the aneurysm at the operating table were positive for *Salmonella cholerae variant suis*. The immediate postoperative course was uneventful. Normal pulses were palpable in both lower extremities. On the third postoperative day he began to

exhibit multiple daily elevations of temperature. Since no specific cause for this febrility could be determined, it was concluded that it represented infection and reaction about the graft site. Numerous blood cultures were sterile, but on a few occasions *Staphylococcus albus* and *Staphylococcus aureus* coagulase negative were reported. Despite vigorous antibiotic therapy, including 30 million units of penicillin intravenously daily, febrility continued until the twenty-seventh postoperative day.

Fig. 2.

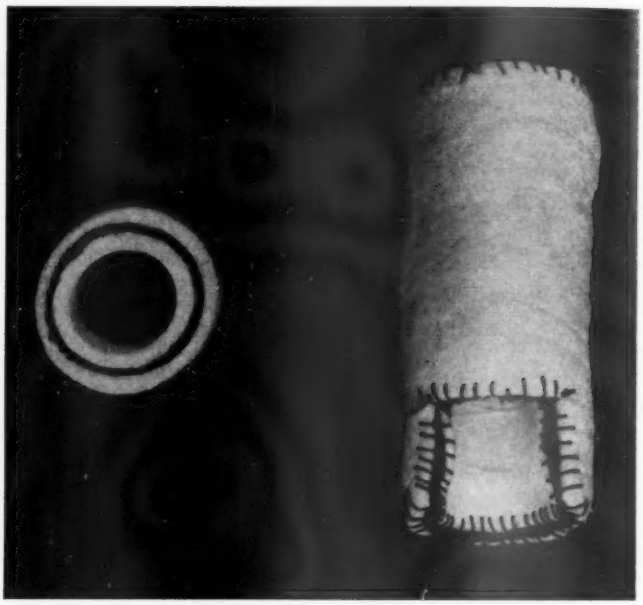

Fig. 3.

Fig. 2.—Artist's drawing of the vascular prosthesis sutured in place. The duodenal opening has been closed.

Fig. 3.—Photograph of a prosthesis of similar material to that used in this patient. It consists of inner and outer layers of Ivalon and a middle layer of Teflon cloth. Before making the anastomoses the 3 components of the prosthesis are sutured together at each end with continuous 5-0 silk to prevent possible separation of the layers.

On the thirty-fourth postoperative day, he developed sudden left lower abdominal pain with progressive dullness and fullness in this area. Peritoneal tap in the left lower quadrant yielded dark blood. The patient was returned to the operating room and an initial thoracotomy was performed to obtain control of the proximal aorta. At laparotomy a large left retroperitoneal hematoma was found secondary to a small leak in the anastomosis between the graft and the left common iliac artery. There was no gross evidence of infection anywhere within the abdomen. The anastomotic leak was easily repaired and the immediate postoperative course was satisfactory, although re-expansion of the left lung was somewhat slower than usual. On the third postoperative day the patient developed clinical signs of a left cerebrovascular accident and became semicomatose. Despite tracheostomy and the usual conservative measures, he rapidly deteriorated and expired on the fifth postoperative day. Permission for autopsy was not granted.

DISCUSSION

In 1943, Rottino[14] found 31 cases of rupture of abdominal aortic aneurysms into the gastrointestinal tract previously reported in the literature and added one. Hunt and Weller[9] added 9 cases, including one of their own. Since then,

an additional 21 patients have been recorded.[1-3, 5-8, 10, 12, 13, 15] This report brings the total to 63, including one instance[6] in which no actual communication between the lumen of the bowel and the aneurysm was demonstrable at autopsy.

The ages ranged from 20 to 81 years; approximately 64 per cent occur beyond the fifth decade (Table I). Males predominated in a ratio of 3 to 1. In 49 instances (77.7 per cent), rupture occurred into the duodenum, and, of these, 41 involved the third part of the duodenum (Table II). This frequent involvement of the third part of the duodenum is believed attributable to its close fixation to the anterior aortic wall.

TABLE I. AGE INCIDENCE

AGE IN YEARS	NUMBER OF CASES
11-20	1
21-30	5
31-40	6
41-50	7
51-60	14
61-70	12
71-80	13
81-90	2
Not stated	3
Total	63

TABLE II. SITE OF ANEURYSMAL RUPTURE

LOCATION	NUMBER OF CASES
Stomach	7
Duodenum	49 (77.7%)
First part	1
Second part	1
Third part	41 (65.1%)
Not stated	6
Jejunum	5
Small intestine (site not stated)	1
Jejunal mesentery (see text)	1
Total	63

Of the 41 patients in whom the site of aneurysm was stated, the aneurysm arose below the origin of the renal arteries in 31. In 44 cases a palpable abdominal mass was present; the mass was pulsatile in 37 of these. In only 9 instances was the mass reported to be tender.

A significant factor noted in a review of these patients is the time interval between the initial episode of gastrointestinal bleeding and death (Table III). In only 17 cases (27 per cent) did death occur within 6 hours of the onset of bleeding. In 25, this interval was from one day to 2 weeks. In 4 patients the interval was one month or longer; the longest was 6 weeks. For those in whom the interval is 6 hours or longer, prompt surgical intervention might be lifesaving. From these data, it would appear that, from the standpoint of sufficient time, surgical therapy might be applicable to 60 per cent of those having an abdominal aortic aneurysm rupture into the gastrointestinal tract. In three-fourths of the reported cases, the aneurysm arose below the origin of the renal

vessels and may have been surgically correctable. Theoretically then, in about 45 per cent of these patients, it should be possible to explore and surgically to correct the condition, provided the diagnosis can be established.

TABLE III. INTERVAL BETWEEN ONSET OF INITIAL BLEEDING AND DEATH

LENGTH OF TIME	NUMBER OF CASES	PER CENT
Less than 6 hours	17	27.0
6 to 24 hours	9*	14.3
More than 24 hours	29	46.0
Not stated	8	12.7
Total	63	100.0

*Includes the present case report, the length of time in this instance being the interval between the onset of bleeding and the time of operation.

In no previously reported case was the aneurysm attacked surgically, and only 2 patients underwent laparotomy, one[4] for abdominal pain in whom no definitive surgery was carried out and one[15] because of gastrointestinal bleeding for which a subtotal gastric resection was performed.

Symptoms of abdominal aortic aneurysm include abdominal pain which may be cramping or constant, sometimes referred to the hip, leg, or scrotum. Pressure of the aneurysm on the vertebrae is characterized by an articular-type back pain; on the gastrointestinal tract by indigestion, nausea, vomiting, intestinal obstruction and weight loss; and on the genitourinary tract by oliguria and anuria.[1] Rupture into the gastrointestinal tract results in hematemesis and melena of varying degrees with the attendant findings of blood loss. A pulsating, expansile mass with thrill and murmur may be present; tenderness over the mass may indicate imminent or actual rupture. Roentgenograms may show a calcified abdominal mass with vertebral erosion. Rupture is often associated with a marked leukocytosis and a moderate elevation of the diastase content of the urine.[11]

It is suggested that, in a patient with massive bleeding into the gastrointestinal tract, whose history and signs indicate the presence of an abdominal aneurysm, the possibility of the aneurysm having ruptured into the duodenum or other portion of the gastrointestinal tract should be entertained. Particularly when rupture of the aneurysm is further suggested by tenderness over the pulsatile abdominal mass, surgical exploration with resection of the aneurysm should be seriously considered since this condition untreated is presumed to be uniformly fatal.

SUMMARY AND CONCLUSIONS

1. Sixty-two previously reported cases of rupture of an abdominal aortic aneurysm into the gastrointestinal tract are briefly reviewed, and the sixty-third case is presented. In the previous reports, no instance was found in which surgical excision of the aneurysm was attempted.

2. In more than 60 per cent of these patients, the time interval between the onset of gastrointestinal bleeding and death was sufficiently long to allow surgical intervention.

3. In cases of upper gastrointestinal bleeding with findings consistent with abdominal aortic aneurysm, rupture of the aneurysm into the gastrointestinal tract should be suspected, particularly if the aneurysm is tender.

4. With the vascular surgical techniques now available, early surgery should be considered for those in whom this diagnosis is strongly suspected since almost half of these patients are theoretically salvagable by surgery.

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PULMONARY ARTERIOVENOUS FISTULAS IN MOTHER AND SON WITH LIVER ABSCESS COMPLICATIONS IN MOTHER

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THE hereditary tendency and relation of pulmonary arteriovenous fistulas to familial telangiectasia (Rendu-Osler-Weber disease) have become well known. The high incidence of complications, brain abscess, cerebrovascular accidents, and hemoptysis, has also been recognized. There is also general agreement that the morbidity and mortality of the complications constitute greater threats to the patient than the risk of surgical excision of the fistula.[13]

A liver abscess with rupture through the diaphragm, lung, and bronchus associated with a pulmonary arteriovenous fistula has not to our knowledge been previously described. Failure to x-ray the chest of the members of the family of a patient who had had surgical excision of a pulmonary arteriovenous fistula of the anterior basal segment of the left lower lobe (previously reported[12]) resulted in overlooking the diagnosis of pulmonary arteriovenous fistula in the mother. The symptoms produced by the liver abscess brought the mother of this patient into the hospital; surgical drainage of the liver abscess and excision of a segment of the lower lobe containing the fistulous communication to the right bronchus were curative. Subsequently, excision of the pulmonary arteriovenous fistula by posterior basal segmental resection was performed and constitutes the reasons for this report.

CASE REPORTS

CASE. 1. *Asymptomatic Pulmonary Arteriovenous Fistula, Medial Basal Segment, Left Lower Lobe.*—A 22-year-old sailor was referred for angiocardiography on Jan. 17, 1956. Routine chest roentgenography had disclosed a rounded 3 by 3 cm. density, in the medial basal segment of the left lower lobe which was connected to the left hilum by vessels (Fig. 1, *A* and *B*). On physical examination there was a systolic (grade 3) bruit near the apex of the heart which was accentuated with inspiration; elsewhere there were no abnormal findings. A familial history of bleeding or telangiectasia was denied; examination of the members of the family was not made. Laboratory data revealed hemoglobin, 15.0 Gm./100 c.c., and hematocrit, 50 per cent; arterial oxygen saturation was normal.

Angiocardiography (Fig. 1, *C* and *D*) clearly demonstrated an arteriovenous fistula confined to the medial basal segment of the left lower lobe. On Jan. 19, 1956, the medial basal segment of the left lower lobe containing the arteriovenous fistula was excised and the patient made an uneventful recovery.

CASE 2. *Hereditary Capillary Telangiectases (Rendu-Osler-Weber Disease) and Pulmonary Arteriovenous Fistula, Left Posterior Basal Segment, Complicated by Liver Abscess With Bronchopulmonary Fistula and Transient Left Hemiplegia.*—A 47-year-old housewife, the

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mother of the patient in Case 1, was admitted on Sept. 25, 1956, with complaints of cough, expectoration, and fever. A year prior to admission, the patient had developed suddenly severe right anterior chest pain and fever. She was confined to a hospital for 8 days, given antibiotics, and told that she had pneumonia. After discharge, although the chest pain subsided, low-grade intermittent fever persisted despite antibiotic therapy. Seven months prior to admission, while bouncing a granddaughter on her lap, she experienced a "bursting" sensation in

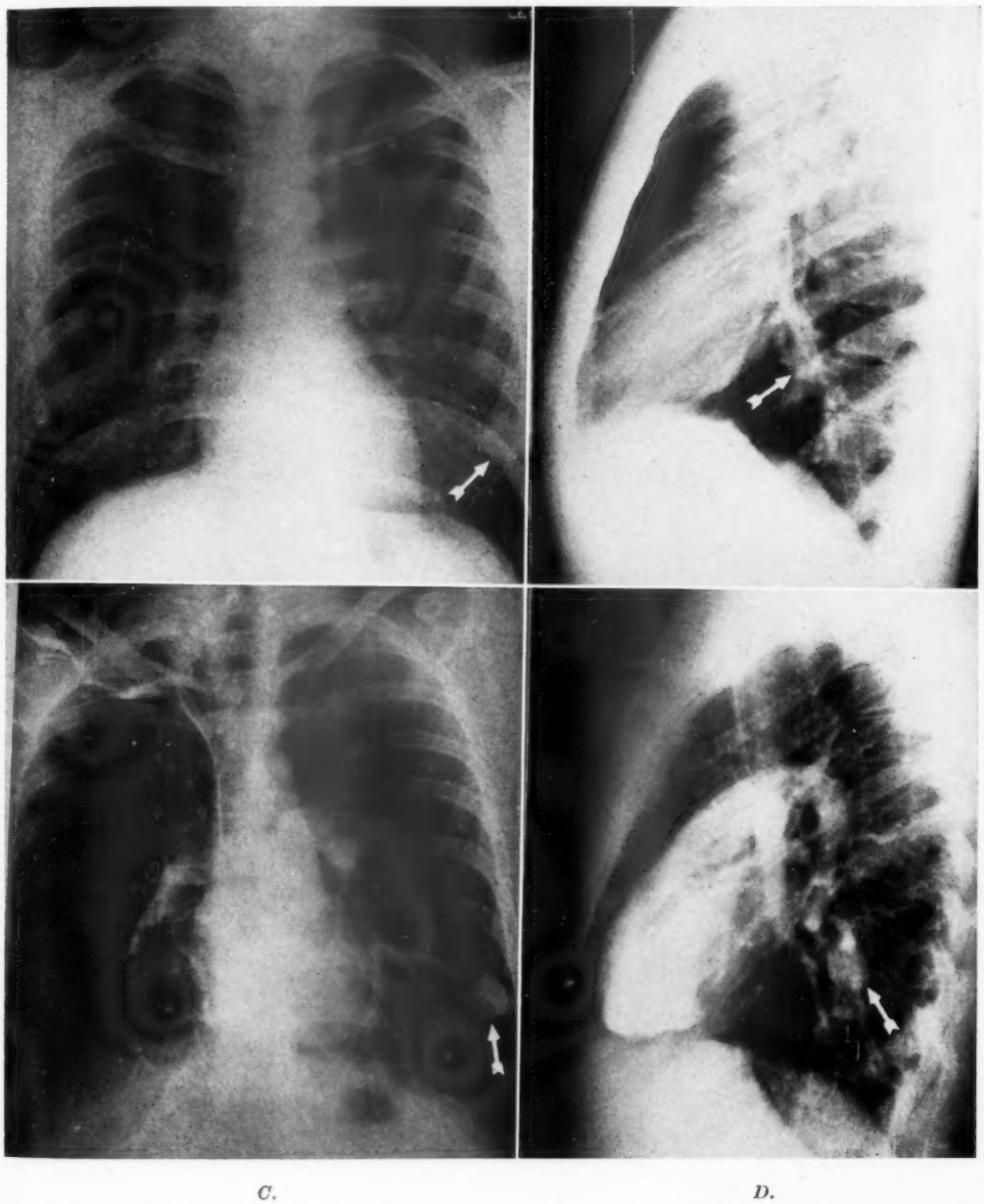
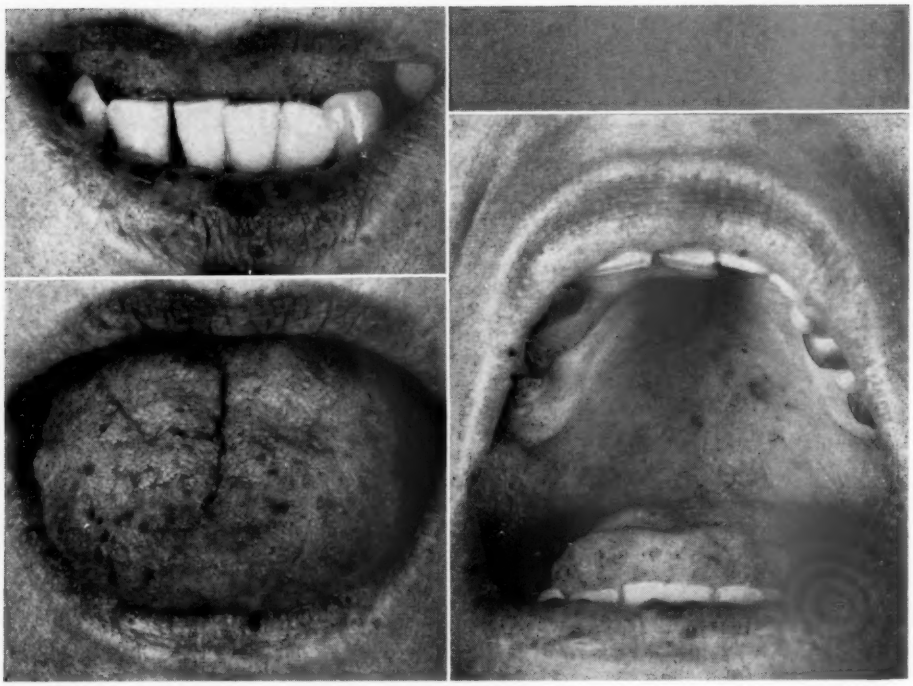


Fig. 1.—Case 1. *A*, Conventional frontal roentgenogram shows a rounded mass left lower lung field (arrow) with vascular connections to the hilus. *B*, Lateral view shows the mass to be located in the medial basal segment of the left lower lobe. *C*, Frontal angiocardiogram clearly shows the vascular nature of the pulmonary arteriovenous fistula (arrow). *D*, Lateral angiocardiogram localizes the pulmonary arteriovenous fistula in the medial basal segment of the left lower lobe. (Reproduced with permission from Am. J. Roentgenol.[12])

the right lower chest followed by coughing of brown, foul-smelling material which was described as "tasting like liver." From then on, there was daily cough and expectoration of about 20 c.c. of purulent material. Bouts of fever persisted and became continuous 3 weeks prior to admission.

A.



B.

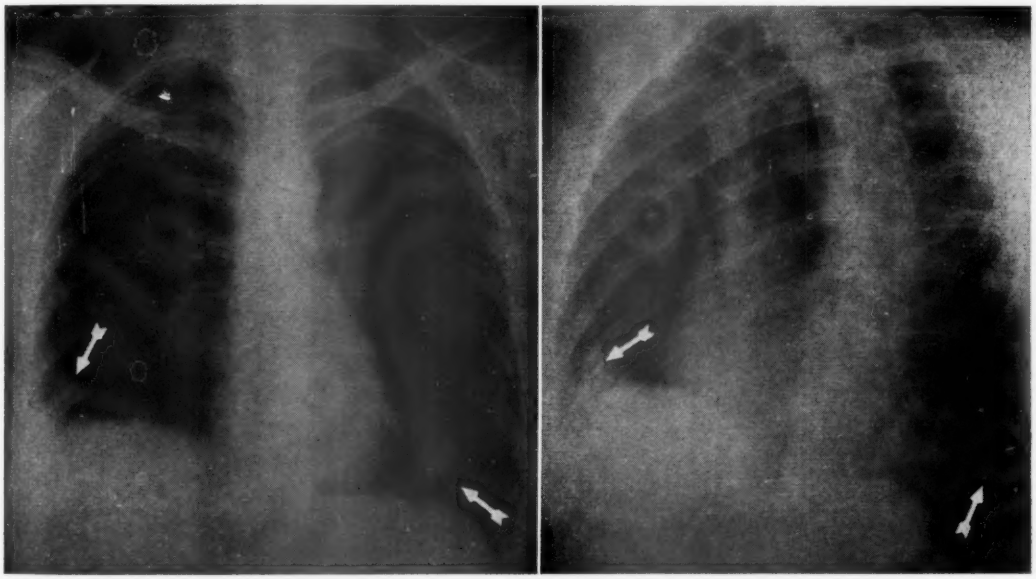
C.

D.

Fig. 2.—Case 2. *A*, Photograph showing capillary telangiectasis of the cheeks and lips. *B*, Enlarged view of telangiectasia of the lips. *C*, Photograph showing multiple telangiectasia of the tongue. *D*, Photograph reveals scattered telangiectases of the palate.

All her life the patient had had nose bleeds and was aware of dilated vessels of the lips. Her mother, age 77 years and still living, also had had nose bleeds, anemia, and dilated vessels of the lips. A brother died of a cerebrovascular accident at the age of 35 years. Examination of the patient's mother, brother, and her daughter showed telangiectasia of the mucous membranes and skin of only the patient's mother. The chest x-rays of all 3 did not show pulmonary arteriovenous fistulas.

Examination of the patient showed capillary hemangiomata of the face (Fig. 2, *A*), lips (Fig. 2, *B*), tongue (Fig. 2, *C*), mucous membrane of the roof of the mouth (Fig. 2, *D*), and nose. There were moist râles at the base of the right lung. A bruit was heard along the base of the left lung posteriorly. Mild clubbing of the fingers without cyanosis was present. There were no cardiac murmurs; the blood pressure was 120/80 mm. Hg. X-ray examination of the chest (Fig. 3, *A*) revealed elevation of the right diaphragm with obliteration of the right costophrenic angle and haziness of the outer portion of the right lung. A rounded mass 3.0 by 2.5 cm. in diameter was present at the left base and was located in the posterior basal segment of the left lower lobe (Fig. 3, *B*). The heart was not enlarged. Angiocardiography was done in frontal and left anterior oblique positions on Sept. 27, 1956, and disclosed a pulmonary arteriovenous fistula in the posterior basal segment of the left lower lobe (Fig. 4, *A* and *B*). Blood examination showed: hemoglobin, 13.6 Gm./100 c.c.; erythrocytes, 4.2 m./c.mm.; hematocrit, 39 per cent; and a leukocyte count of 10,800 c.mm. The electrocardiogram was normal.

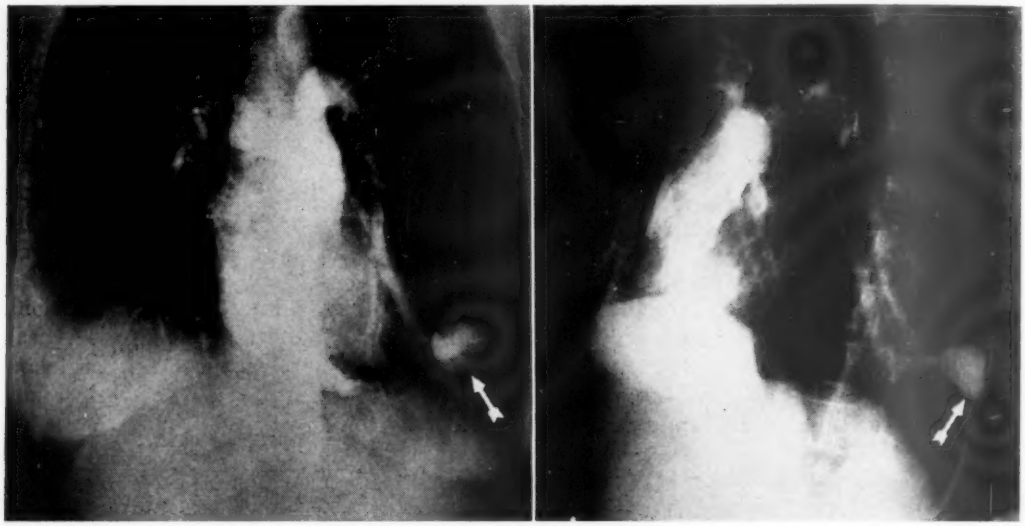


A. *B.*

Fig. 3.—Case 2. *A*, Frontal roentgenogram of the chest shows obliteration of the right costophrenic sulcus; above, there is parenchymal haziness (arrow). A dense rounded mass (arrow) is seen near the apex of the heart. *B*, Left anterior oblique view shows a patch of haziness along the outer lower part of the right thorax (arrow). At the outer and lower edge of the left chest there is also a rounded nodular-appearing mass.

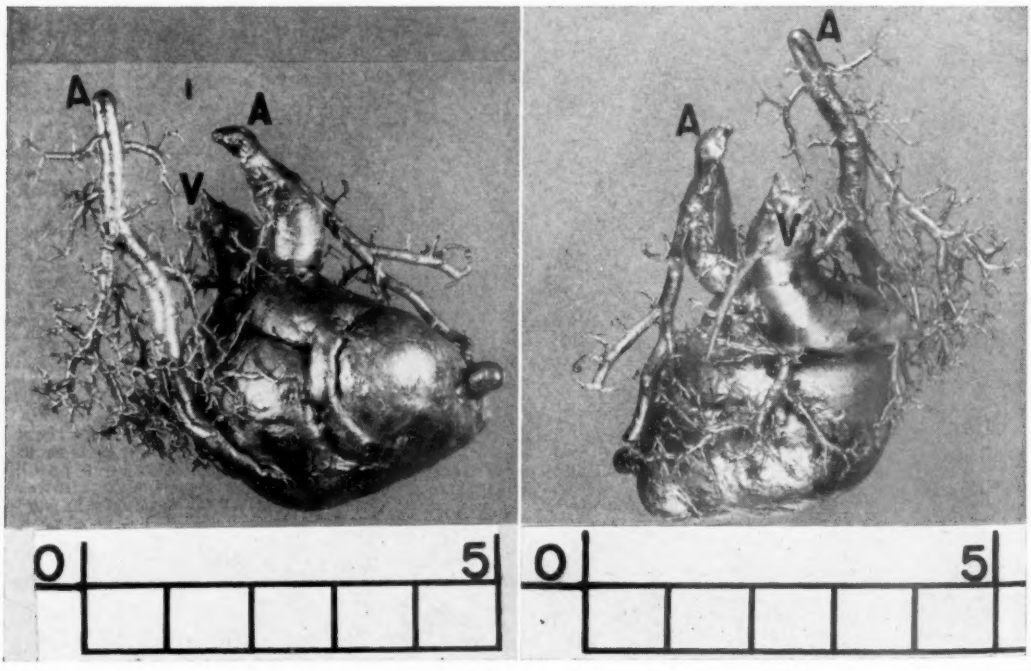
On Oct. 1, 1956, 6 days after admission, the patient awoke with weakness of the left side of the face and hand. Neurologic examination disclosed left facial muscle weakness, slurring of speech, and diminished reflexes of the left side of the body. These findings gradually subsided during a 2-hour period and did not recur. On Oct. 8, 1956, exploration of the right thorax disclosed a pulmonary bronchial fistula communicating with a liver abscess. Exteriorization with drainage and packing of the liver abscess through the chest wall was instituted. A small segment of the right lower lobe containing the pulmonary bronchial fistula was resected and the stump was closed with interrupted silk sutures. The thorax

was drained with 2 tubes through an incision separate from that of the liver abscess. On the third postoperative day, removal of the gauze packing from the liver abscess was begun and completed on the fifth day. Following, tube drainage was instituted. Healing was uneventful and the patient was discharged on the thirteenth postoperative day.



A. *B.*

Fig. 4.—Case 2. *A*, Frontal angiocardiogram shows the pulmonary arteriovenous fistula. Note 2 afferent segmental arteries to the fistula. *B*, Left anterior oblique angiocardiogram shows the pulmonary arteriovenous fistula to be located in the posterior basal segment of the left lower lobe.



A. *B.*

Fig. 5.—Case 2. Metallic cast of fistula, courtesy of Dr. F. Stephen Vogel. *A*, Frontal view. *B*, Posterior view. *A* is the artery; *V*, the vein. Note that there are 2 afferent segmental arteries to the fistula.

Following an uneventful convalescence during which clubbing of the digits disappeared and the patient became asymptomatic, she was readmitted for excision of the left lower lobe pulmonary arteriovenous fistula. On April 16, 1957, the posterior basal segment was excised. Fig. 5 is the anterior and posterior view of the low-melting metal alloy specimen of the excised arteriovenous fistula made by Dr. F. Stephen Vogel. Again, the patient made an uneventful recovery and was discharged on April 28, 1957. Blood studies prior to and after operation showed normal hemoglobin, erythrocytes, and hematocrit findings.

DISCUSSION

In recent years, the literature of pulmonary arteriovenous fistulas has been thoroughly reviewed[12, 13] and so will not be repeated. It has become apparent that pulmonary arteriovenous fistulas are hereditary and closely related to familial telangiectasia (Rendu-Osler-Weber disease). Several sets of siblings,[2, 3, 9, 10] a father and son,[14] a daughter and probably father,[11] and a mother and son[5] with pulmonary arteriovenous fistulas have been reported. It follows, therefore, that the discovery of a case with pulmonary arteriovenous fistula should initiate the routine study and search for other cases in the family. Had this been done in Case 1, the mother (Case 2) might have been diagnosed and treated before the development of a liver abscess.

Earlier, the reports of pulmonary arteriovenous fistulas emphasized the occurrence of dyspnea, cyanosis, clubbing of the fingers, and polycythemia.[3, 11] Later, with increasing experience, asymptomatic cases were discovered after routine roentgenography of the chest and these were found to outnumber the first group.[13] The realization that cerebral complications (brain abscess, cerebral thrombosis, and meningoencephalitis) are frequent in patients with pulmonary arteriovenous fistulas emphasizes the importance of diagnosis of the chest lesion.

The diagnosis of pulmonary arteriovenous fistula can often be made by conventional roentgenography, particularly if the index of suspicion is high. Pulmonary densities with hilar vascular connections localized in lobes or segments of the lung or increased hilar vascularities should arouse suspicion of an arteriovenous fistula. Change in size of the lesions after respiratory maneuvers (Valsalva, Müller) and delineation of the afferent arterial and efferent venous connections by body section radiography may be confirmatory. The finding of a bruit over the lesion is, of course, significant. Angiocardiography, however, definitively establishes the diagnosis of pulmonary arteriovenous fistulas and is recommended for preoperative evaluation (Figs. 1, *C* and *D*; 4, *A* and *B*). In capillary telangiectasis of the lungs, however, angiocardiography may fail to demonstrate the lesion.[1, 4]

A glance at the metallic cast of the excised pulmonary arteriovenous fistula of Case 2 made according to the technique of McClenahan and Vogel[8] will readily reveal that the paper-thin, easily ruptured globular saclike fistula contains not only afferent pulmonary arteries and an efferent vein but many segmental vascular communications. Other types of injection corrosion techniques may also reveal the bizarre nature of the fistulas.[4, 7] Because of large

and multiple arteriovenous communications, the cleansing and sieving functions ordinarily performed by an intact pulmonary arterial capillary bed are lost. Noxious agents, particularly bacterial, may, therefore, lodge in organs supplied by systemic arteries such as the brain and liver and give rise to abscesses. It is mainly for this reason and also to avert fatal hemoptysis[6] that surgical excision of pulmonary arteriovenous fistulas is recommended as a prophylactic measure.

The treatment of pulmonary arteriovenous fistulas is surgical excision with preservation of as much lung tissue as possible in order to save pulmonary function, especially if multiple lesions are present. Surgery is usually curative. It is recommended even in the asymptomatic case since the risk of brain abscess, fatal hemoptysis, or development of cerebral thrombosis, especially if polycythemia occurs, is far greater than the morbidity and mortality of lobectomy or segmental resection.[12, 13]

SUMMARY AND CONCLUSIONS

Pulmonary arteriovenous fistulas in a mother and son, both treated by segmental resection of the lesion in the left lower lobe are reported. The son was asymptomatic and discovered after a routine chest x-ray. Eight months later, the mother, with characteristic capillary telangiectasia (Rendu-Osler-Weber disease) and a segmental left lower lobe pulmonary arteriovenous fistula, was found to have a liver abscess which had ruptured through the right diaphragm and formed a fistulous communication with the right lung and bronchus. Following a transient left hemiplegia, surgical incision and drainage of the liver abscess and pulmonary bronchial fistula resulted in cure of the liver and pulmonary suppuration. Seven months later, the pulmonary arteriovenous fistula of the posterior basal segment of the left lower lobe was excised.

It would appear that excision of pulmonary arteriovenous fistulas is indicated not only for prevention of cerebral complication and fatal hemoptysis but also to prevent peripheral abscesses.

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ADDENDUM

Since this paper was submitted for publication, another report of pulmonary arteriovenous fistula in mother and son has been published. (Beno, T. J., and Das, R.: Familial Arteriovenous Aneurysm of the Lung: Incidence in Mother and Son, Ann. Surg. **146**: 830, 1957.)

Reappraisal

CONDUCTED BY CLARENCE DENNIS, M.D. ASSISTED BY ALFRED HURWITZ, M.D.

VENOUS SHUNT PROCEDURES FOR PORTAL HYPERTENSION IN CHILDREN

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IN 1952, we reviewed the problem of portal hypertension in children associated with upper gastroesophageal hemorrhage.[1] Twenty-one cases were reported. Some received no specific treatment. Operative therapy was carried out in the others. The results of splenectomy, esophagogastrectomy, devascularization of the esophagus and upper stomach combined with vagotomy and gastrojejunostomy, and venous shunt procedures were presented.

Eight procedures in which the portal venous system was anastomosed to the systemic venous system were performed. There were no operative nor postoperative deaths. At that time, 6 patients were considered to have had an excellent result. It was our impression that the venous shunt procedures gave reasonably good results and were to be recommended for the initial treatment of these children. We recognized that the periods of observation following treatment were relatively short. Furthermore, we anticipated that, because of the small size of the splenic and renal veins in young children, the incidence of postoperative occlusion of the shunt might be disappointingly high. Since the time of the original report, 2 additional venous shunt procedures have been performed in children. The present report is a reappraisal of the problem.

Nine patients were treated and 10 operations were performed (Table I). Following the 10 operations, upper gastroesophageal bleeding recurred in 7 instances. Additional operative procedures were attempted or performed in 4 patients and 3 of the 4 eventually died. In 2, bleeding has recurred recently and further operative therapy, though planned, has not yet been carried out. Three patients, listed as Cases 3, 5, and 7, have had no recurrence of bleeding after operation. Two have been followed for over 8 and one for over 6 years. It is of interest that the ages of these patients at the time of operation were 11, 13, and 14 years, respectively. In these 3, it was the impression of the operator that the splenic and renal veins were large enough to permit an anastomosis of adequate size.

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TABLE I. RESULTS OF VENOUS SHUNT PROCEDURES IN CHILDREN

CASE NUMBER	DATE OF OPERATION	AGE AT OPERATION	TYPE OF OPERATION	RESULT
1	1951	6½	Mesenteric to right renal vein	Bleeding recurred in 3 years, died after emergency esophagectomy in 1954
2	1949	11½	Splenectomy and splenorenal shunt	Bleeding recurred in 1 year, devascularization of esophagus in 1950, bleeding recurred in 5 months, died during attempted emergency esophagogastrectomy in 1950
3	1949	11	Splenectomy and splenorenal shunt	No recurrence of bleeding for over 8 years
4	1949	2	Splenectomy and splenorenal shunt	Bleeding recurred in 2½ years
	1951	4½	Portacaval shunt	Bleeding recurred in 7 months, died after emergency esophagogastrectomy in 1952
5	1949	13	Splenectomy and splenorenal shunt	No recurrence of bleeding for over 8 years
6	1949	4½	Splenectomy and splenorenal shunt	Bleeding recurred in 2 years, esophagogastrectomy in 1952, no recurrence of bleeding in 6 years
7	1951	14	Splenectomy and splenorenal shunt	No recurrence of bleeding for over 6 years
8	1956	12	Splenectomy and splenorenal shunt	Bleeding recurred in 1¼ years
9	1957	8	Splenectomy and splenorenal shunt	Bleeding recurred in 6 months

All who were operated upon before they were 11 years of age had recurrence of bleeding. In 2, who were operated upon at the ages of 11½ and 12 years, bleeding occurred again. Death occurred in 3 either during or shortly after emergency esophagogastrectomy performed for severe upper gastroesophageal hemorrhage. In one, death occurred from cardiac arrest and shock during the attempted procedure; in another, death followed perforation of a gangrenous small bowel loop. The strangulation obstruction was due to adhesive bands in the peritoneal cavity. Because of the severe upper gastroesophageal bleeding, the signs and symptoms of the bowel obstruction were obscured. The third patient developed an esophagopleural fistula and empyema; however, her death was due to massive recurrence of upper gastroesophageal hemorrhage a few days after esophagogastrectomy. Autopsies disclosed a thrombosed splenic vein in 2, and, in the third, the anastomosis could not be identified.

At present, it would appear that splenectomy and splenorenal shunts performed in children who have portal hypertension with esophageal varices and upper gastroesophageal bleeding will give reasonably good results only if the splenic and renal veins are of sufficient size to permit a relatively large anastomosis. If these structures and the resulting anastomosis are small in

size, bleeding will probably recur. These circumstances tend to prevail in children under 11 years of age. Esophagogastrectomy performed as an emergency procedure for bleeding esophageal varices is attended with a high mortality. Transesophageal ligation of the varices would, undoubtedly, be better tolerated.

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Appraisal of Progress in Surgical Therapy

CONDUCTED BY WARREN H. COLE, M.D.

HYPOTHERMIA

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CLINICAL hypothermia has now been in use for 5 years. There are limitations to its use which are imposed by the fact that one cannot reduce the body temperature of humans, with safety, below approximately 28° C. Actually, there seems to be an increase in risk between 30° and 28° C., so that currently a somewhat higher temperature level of 30° C. is a more popular and safe operating temperature. At this level the oxygen requirements are a little less than 50 per cent of normal. Judging from experimental work one would expect infants, and especially newborns, to tolerate much lower body temperature. It is interesting that, in spite of 7 years' extensive experimental research on the part of many university centers, the knowledge gained from this has not lowered the useful range of temperature appreciably, although it has made this therapeutic range more safe.

CURRENT USES OF HYPOTHERMIA IN VASCULAR SURGERY

Hypothermia was originally designed to allow intracardiac surgery under direct vision. However, since the patient can only be cooled with reasonable safety to the 28° to 31° C. body temperature range, this allows the circulation to be totally interrupted for 5 to 6 minutes with reasonable safety. Actually, I have been using elective cardiac arrest and it would appear that periods of interruption up to 10 minutes are tolerated with no brain damage. Six such patients have had circulation interrupted between 7 and 11 minutes. It was previously felt that the brain was just as sensitive as the heart to the interruption of the circulation. However, current clinical work on the use of hypothermia in neurosurgery stimulated the concept of using elective cardiac arrest on the theory that the brain will tolerate interruption for a few minutes longer than the heart, and especially an abnormal or enlarged heart. This extra time has not increased the scope of clinical conditions which may be corrected under direct vision with hypothermia, but it has made the correction an unhurried surgical procedure that can be carried out more accurately and more satisfactorily.

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The operations currently performed under direct vision are well known. They represent simple lesions that can be corrected in this length of time. Interatrial septal defects, congenital aortic stenosis, congenital pulmonary stenosis, anomalous pulmonary venous drainage, and ruptured aneurysm of the sinus of Valsalva represent the majority of clinical conditions correctible by this technique.

Hypothermia may be used as an adjunct in the surgery of very poor-risk patients. It is felt that this use of hypothermia has not been adequately explored. It is difficult, or impossible, to perform most standard heart operations both in the acquired and congenital heart disease group without inducing some degree of hypoxia. This may be produced by a fall in blood pressure, a reduction in the aerating surface of the lung, which is usually required to give exposure, or by direct manipulation of the heart. Partial occlusion of the circulation is necessary to complete some of the operations for congenital heart disease.

When one engages a valve orifice with the finger or an instrument, one partially, or totally, interrupts the circulation; thus the principle in using hypothermia as an "adjunct" is the same as that for intracardiac surgery. The periods of interruption of the circulation are shorter but they are usually repeated and in very poor-risk patients are poorly tolerated.

Although I have used hypothermia as an adjunct in a variety of conditions, the only thing resembling a controlled series is a group of cases of terminal mitral stenosis in chronic failure with multivalvular lesions. In two groups of similar severity the operative risk has been reduced from 43 to 19 per cent with the use of hypothermia.

The brilliant surgical results of treatment of ruptured cerebral aneurysms using hypothermia and local interruption of the circulation to the brain are well known. It is still probably the method of choice in uncomplicated thoracic aneurysms and certain other lesions involving major branches of the aorta.

THE CURRENT RELATION OF HYPOTHERMIA TO CARDIAC BYPASS

Currently the use of hypothermia for intracardiac surgery in simple lesions is being challenged by the technical improvements in the heart-lung pump. The issue may be interpreted, at present, in this manner. With hypothermia, for the correction of these simple defects just listed, one has a technique which is safer than the extracorporeal circulation and less tedious, but the operator has a time limit and as stated he would not be in a position to correct associated lesions if these were unexpectedly encountered at operation. This criticism is less valid with 7 to 10 minutes' interruption allowed by elective cardiac arrest. Perhaps the answer to the problem lies in the excellence of the preoperative diagnoses which are supplied to the surgeon.

Those favoring the heart-lung pump for use in all intracardiac lesions, including the simple ones, conversely state that they are prepared for any eventuality once the heart is opened and that their work may be less hurried. Some centers with longer experience point out that the actual risk of the pump

and circulatory bypass is an acceptable one. When the Minneapolis group recently reported their last 40 consecutive cases, including atrial septal defects, with one death, one must remember that their over-all published mortality rate in congenital heart operations in over 300 cases is about 40 per cent. Their technical experience and "know-how" cannot be duplicated by a team in the early stages of cardiac bypass surgery. It is quite likely that when the technique of extracorporeal circulation becomes even safer than it is at present, or when all centers have had adequate experience with bypass surgery, this argument will be solved. Until then it is suggested that there will be proponents of both techniques.

Until we have a method of replacing valves and a sure method of revascularizing the heart, both hypothermia and cardiac bypass surgery will have a limited application in acquired heart disease.

TECHNIQUE

There are several cooling and rewarming techniques and methods of supplemental anesthesia which have been tested over the last few years. I feel that surface cooling is the most practical in cardiac surgery, and in children it is best done by immersion in a cold bath, whereas adults are cooled just as efficiently with the use of cooling blankets, ice bags, and air conditioning control over the operating room temperature. In the range of temperatures used in most centers now, a body temperature of approximately 30° C., no special rewarming measures are needed. However, it is worth while to have available a radiofrequency rewarming device, a water bath, or both, in case rapid rewarming is required to control an unusual drift in body temperature. An advantage in the blankets for cooling is that the lower blanket can be used to initiate rewarming during the operation and it is best to have rewarming initiated before completion of surgery. There are 3 chief risks to hypothermia of particular importance to the anesthetist and their management might be discussed at this time.

Ventricular Irritability.—The best control of this is by insuring that the body temperature does not go below 28° C. and in adults preferably very little below 30° C. Although most anesthetists relate ventricular irritability to a low blood pH, a recent study by Wadell has demonstrated that a more important cause is the level of blood citrate and that irreversible ventricular fibrillation is seldom encountered when one uses heparinized blood and does not have to contend with the citrate-calcium balance. A low pH may play a part but it is possible that patients with a low pH have been those in whom difficulties have been encountered and a large quantity of citrated blood has been used. This could lead to the erroneous assumption that irritability is directly and solely related to pH.

Bleeding Tendency.—The only hematologic observation during clinical hypothermia to explain the occasional marked bleeding tendency is a thrombocytopenia that develops at low body temperature, then reverts to normal during rewarming. Thrombocytopenia and bleeding tendency would appear to

have been controlled in the last 6 cases I have operated upon in which the patient is heparinized prior to cooling. This is rather a remarkable use for heparin, that is, to control a bleeding tendency. Space does not permit discussion of the experimental basis and rationale of this addition to the hypothermia technique.

Rewarming Shock.—Shock and sometimes death during the rewarming period have been traced to a tendency of the patient to develop a metabolic acidosis. This is likely to develop if the peripheral circulation is not maintained and if steps are not taken to prevent peripheral vascular spasm. The appearance of metabolic acidosis in the form of lactic acid is minimized if the blood supply to the peripheral tissues is maintained with maximum oxygenation.

In practical terms, metabolic acidosis can be controlled with 2 types of anesthetic: (1) the use of chlorpromazine, promethazine, and meperidine drugs, or alternatively, (2) by the use of a modest quantity of ether throughout cooling. The latter technique has proved to be the most practical, since it is simpler and avoids the central depression inherent in the "lytic cocktail" technique.

One should strive for a pH above 7.3 during the entire procedure, cooling and rewarming. It is probably best not to maintain a respiratory alkalosis during the entire cooling but rather in the period immediately prior to interruption of the circulation by increasing the respiratory ventilation and using a carbon dioxide absorber.

THE FUTURE OF HYPOTHERMIA

It is likely that we have not heard the last of hypothermia. In this regard, among the many active fields of research, there are 3 important research projects that may well hold the key to the future of hypothermia.

1. The rapid freezing and resuscitation of small animals by Anjus and Audrey Smith are exciting. This experiment has recently been duplicated and linked to carbon dioxide and pH. It reminds one of the unusual dog coolings of Niazi with manipulation of the carbon dioxide content of the respired air.

To accomplish freezing one must have a small body mass to allow rapid, uniform, cooling without the creation of a significant temperature gradient in the tissues. Another interesting observation is that after these animals have been at near-freezing body temperature for over an hour, the percentage of animals that can be resuscitated is reduced. One would expect, by extrapolating the oxygen consumption graph, that they would tolerate cessation of circulation for several hours. Perhaps such a technique of cooling is unphysiologic, for it is known that a given fall in temperature does not reduce the rate of all biochemical reactions by the same degree. A catalyst to adjust cell metabolism to this new cold environment may be required.

2. A new trend was apparent at a recent meeting in Chicago, sponsored by the American Heart Association. This meeting consisted of representatives of surgical teams interested in extracorporeal circulation both in America

and Europe. Several of the centers reported the combined use of hypothermia and extracorporeal circulation experimentally. The work of Gollen is interesting. He not only combines the two but makes use of this combination to obtain a lower range of body temperature than that which is ordinarily tolerated by the experimental animal.

We know that cardiac bypass cannot be tolerated for much more than an hour and within that time limit the risks of the procedure are becoming controlled. We also know the limtations and have adequate control over the risks of hypothermia. It may be timely to combine these two procedures now.

3. Perhaps the answer lies in hibernation. Newborn animals, including dogs, behave like hibernating animals and can be cooled to within 3 or 4 degrees of freezing and resuscitated by ordinary cooling techniques. The hibernating animal, such as a groundhog, can be cooled to 3° C. and survive total interruption of the circulation for over 2 hours. These facts and many others have prompted me to continue the study of hibernation and the hibernating gland. Perhaps the infusion of some hormone into a human may allow physiologic cooling to a low temperature by altering some phase of cell metabolism. If this could be accomplished without upsetting the orderly relationship of one biochemical reaction to another within the cell, then we would be duplicating the hibernating animal and it would be expected that the circulation could be interrupted for 2 hours or more.

Hypothermia appears to be a simple and physiologic approach to the problem of interrupting the circulation for prolonged periods in human beings. It is quite possible that within the next few years, as a result of current research, prolonged interruption of the circulation at very low body temperatures may be accomplished. It would mean that surgical conditions correctible in one hour and currently treated with cardiac bypass could be operated upon with a lower range of hypothermia. In that event it would occasion considerable readjustment in our current thinking with regard to open heart surgery.

Surgical History

CONDUCTED BY JOHN R. PAINE, M.D.

SOME EVIDENCE OF THE INFLUENCE OF THE DEVELOPMENT OF ASEPTIC TECHNIQUES ON SURGICAL PRACTICE

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"And he shall break down the house, the stones of it, the timber thereof, and all the mortar of the house; and he shall carry them forth out of the city, into an unclean place." Leviticus 14:45.

THE house of the leper was no more greatly feared 1,500 years before Christ than was the hospital 100 years ago. It was more than 1,900 years ago that the "surgeon" Celsus first recorded the cardinal signs of inflammation, calor, dolor, rubor, and tumor, and more than 1,800 years were to pass before succeeding surgeons were to know the cause and attempt the prevention of the inflammatory reaction in surgical wounds.

Our story begins about 100 years ago. Anesthesia had recently been discovered, and the influence of this blessed gift to mankind was already being appreciated by the hospitals and physicians, since the public, like Mr. Venable, "from dread of pain" no longer avoided operations.[2] There was an immediate demand for more surgery at the Massachusetts General Hospital, and in the 5 years following the introduction of anesthesia there was almost a threefold increase in the number of operations performed. But what was gained by freedom from pain during the operation was frequently offset by the terrible suffering from protracted sepsis following operation. Surgery as an art was at its zenith, but as a science it was an infant grasping blindly in a septic world. It is instructive but by no means pleasing to read of the surgeon's fight against sepsis at this time. John Homans, of Boston, wrote "Of my first five unantiseptic ovariotomies, all died. . . . The causes of death have usually been Peritonitis and Septicemia."[12] W. W. Keen, of Philadelphia, described his experiences in graphic detail. "Our methods of performing these dozen operations were simple—and often fatal. Our hands were, as a rule, as clean as those of a gentlemen, but were never disinfected. The patient's skin was similarly clean or cleansed, but not disinfected. . . . Our instruments, from germ-gathering, velvet-lined cases, were laid out on a table—and not disinfected. If they needed a little sharpening, I have—not often, but actually two or three times—seen

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them stropped on the boot, and even on its sole. If an instrument fell on the floor, it was swished in a basin of unsterilized water, and again plunged into the wound without disinfection.''[13] The fatalities following operation were so high that the results ''might well make 'patients, no matter how critical their need, dread the very name of hospital, and the most skillful surgeons distrust their own craft.' ''[23]

What was the nature of this frightful complication? ''Hospitalism'' was the word coined by Sir James Simpson to group ''together all the deleterious influences met with in hospitals—'hospital sore throat,' 'hospital gangrene,' 'hospital plagues' . . . a septic influence capable of infecting a wound . . . (which) commonly exists to a greater or less extent in all hospitals . . .''[11] ''Hospital gangrene'' was not new. Cooper's *Dictionary of Practical Surgery* in 1848 credits the ''first distinct modern account of this disease'' to have been published in the works of Pouteau in 1783. As defined by Cooper, it was ''a severe and peculiar species of human gangrene . . . particularly characterized by its contagious or infectious nature; its disposition to attack wounds, or ulcers in crowded hospitals . . .''[7] Suppuration was expected from wounds, and the cause for it was not at all understood.

Medical education in America 100 years ago was in need of considerable improvement. The only medical book of note available in the immediate pre-Lister period was the two-volume *Surgery* by Gross published in 1859. Some idea of the caliber of the medical student just prior to the introduction of antisepsis can be appreciated from the account of President Eliot of Harvard, who wrote that in about 1870 he proposed ''that written examinations be introduced as one of the measures to raise the standard of medical education, but the professor of Surgery, who at that time had complete charge of the Harvard Medical School, went around to all of the members of the Board of Overseers —he was a man of quick wit, picturesque language, and great personal influence —and told them that this young President was going to wreck the Harvard Medical School; it would cease to exist in a year or two if his revolutionary reconstruction of the School were allowed. 'He actually proposes,' said this professor, 'to have written examinations for the degree of doctor of medicine. I had to tell him that he knew nothing about the quality of the Harvard medical students; more than half of them can barely write. . . .' ''[10]

The ''premedical'' student about 1860 had little scientific training. Weir Mitchell interviewed ''a young man who desired to enroll with him as an 'office student.' In questioning him as to his educational qualifications, Mitchell fortunately asked if he had any 'accomplishments,' whereupon he put his hand to the back of his neck, drew forth a bowie knife, and, without a word, implanted it deftly in the frame of Mitchell's window between two panes of glass. It is needless to add that he was referred to a more martial preceptor.''[13]

We have collected data on the total admissions and deaths in the Pennsylvania Hospital over a 200-year period. We have tried to correlate these data with the changes that took place in the city of Philadelphia or in the world where, for one reason or another, the care of the patients in the Pennsylvania

Hospital might be influenced (Fig. 1). The Pennsylvania Hospital in Philadelphia was prominent in the early medical education in this country. The first medical school in North America, now the University of Pennsylvania Medical School, was founded in 1768, some 14 years after a charter was granted to the Pennsylvania Hospital.

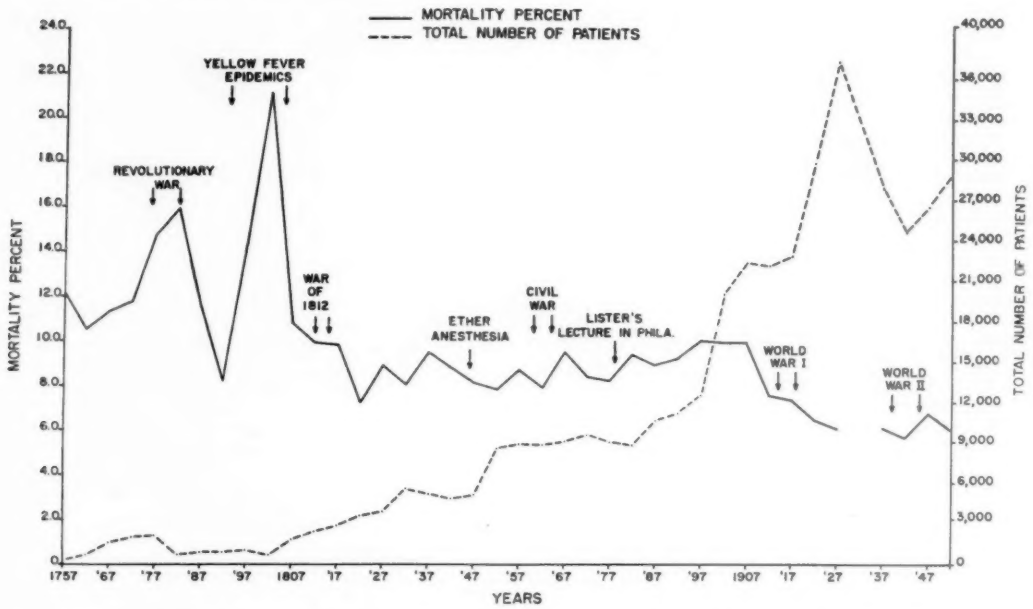

Fig. 1.—Inpatients treated over a 200-year period from 1753 through 1952 at the Pennsylvania Hospital.

During the Revolutionary War the British entered Philadelphia in 1777 and stayed for about one year. During this time they quartered their sick and injured in the hospital. During the yellow fever epidemics a determined effort was made to keep the yellow fever victims out of the hospital, but they were not always successful, as noted in the minutes of the Managers' Meeting dated Aug. 27, 1798. "Yellow fever then raging in the city, there were only three Managers present, whose minds were not reassured when it was ascertained that a patient had died recently in the house of a fever . . ."[16] Also, in Elizabeth Drinker's diary, dated Dec. 12, 1803, there is a note that a servant, Sally Dawson, contracted yellow fever and was sent to the hospital where "she lived but three days after her coming there."[10] During the War of 1812 the hospital admitted prisoners of war, and, again during the Civil War, soldiers were admitted as patients. As noted in Fig. 1 there is no significant decline in the percentage mortality until around the turn of the twentieth century.

One cannot hope to get a true impression of the influence of the development of antisepsis and asepsis on *surgical* mortality from the *total* hospital deaths. The information is of value, however, since it covers a period in excess of the entire existence of our country as an independent nation. One might logically expect to obtain more data on purely surgical problems if we could review the injuries incurred and treated during the various wars.[1] We were not able to find any

figures for the Revolutionary War, but we assume from the following dispatch that life in the army during that struggle was not too "salubrious"! This was a dispatch from Dr. John Bartlett, a surgeon in the field, to Dr. Potts, director of the Military Hospital at Philadelphia. The date was 1777.

"Dear Sir:—

. . . I am this moment returned from Fort Edward, where a party of Hell Hounds, in conjunction with their brethren, the British troops fell on our advance guard, and inhumanly butchered, scalped and stripd four of them and wounded two more, each in the thigh; four more are missing. Poor Miss Jenny McCrea, and the woman with whom she lived, were taken by the savages, led up the hill to where there was a body of British Troops; there the poor girl was shot to death in cold blood, scalped and left on the ground; the other woman not yet found. The alarm came to camp at two P.M.; I was at dinner. I immediately sent off to collect all the Regimental Surgeons, in order to take some one or two of them along with me to assist, but the Divil a bit of one was there to be found, except three mates, one of whom had the squirts; the other two I took with me. There is neither amputating instruments, crooked needle, or tourniquet in all the camp. I have a handful of lint and two or three bandages, and that is all. What in the name of wonder I am to do in case of an attack, God only knows; without assistance, without instruments, without everything. . . .

I am, Sir,
Your very humble servant
JNO. BARTLETT."[16]

The surgeons were not paid very well at that time, receiving but 1⅓ dollars a day.[6] A reference was also made to the employment of nurses, although apparently they did not expect to get any since they offered only 2 dollars a month.[17]

As we pass through the ages, war giving way to war, we see one hopeful sign. The wounded soldier who lived to be treated at long last had an excellent chance of survival (Fig. 2). The highest mortality noted during the Crimean War was believed to be related to the fact that it was a prolonged campaign which was more or less static, and the same surgeons operated day after day with little relief, moving uninterruptedly from wound to wound. The frightful mortality in this conflict for gunshot wounds of the thigh resulting in amputation was about 65 per cent for the English Army and about 92 per cent for the French. That is, in the French Army, 1,531 of 1,666 amputees died.[10] Matters did not improve much by the time of our Civil War. Keen wrote of "what dreadful results followed our best treatment in those days. Tetanus killed almost 90 per cent of its victims, and blood poisoning . . . killed 97.4 per cent. Hospital gangrene—what fierce irony in the very name!—was frequent and had a mortality rate of 45.6 per cent."[1] He also said that during the Civil War but a *single* wound of the small intestine recovered.

At about this time another great battle was being waged in civilian life. Although Oliver Wendell Holmes in 1843 and Semmelweiss in 1847 had fought, all their hearts could stand, for cleanliness in the care of the woman in labor, the battle of puerperal fever was still to be won. In 1856 at the Paris Maternite, 64 of 347 mothers died, and in 1864 in Paris, 310 of 1,350 mothers died.[13] It

was not to be until 1879 that a great man was to rise from his seat at the Paris Academy and go to the blackboard to carefully trace the killer for all to see. "'Voila!'" said he, "'*That* is what it is like!'"[13]

Pasteur "laid the foundation of biological chemistry and proved that spontaneous generation did not exist but were fermentations already due to living organism." Lister immediately appreciated the importance of the discoveries of Pasteur to surgery. "He was watching on the heights and he was watching there alone" (Allbutt). It is not known if Lister's early experience with antisepsis had any immediate effect in America. The Germans tried it out in Volkmann's clinic[20] and in von Bergmann's clinic. The idea was confirmed and actually the gradual evolution of aseptic technique is due in large part to their efforts.

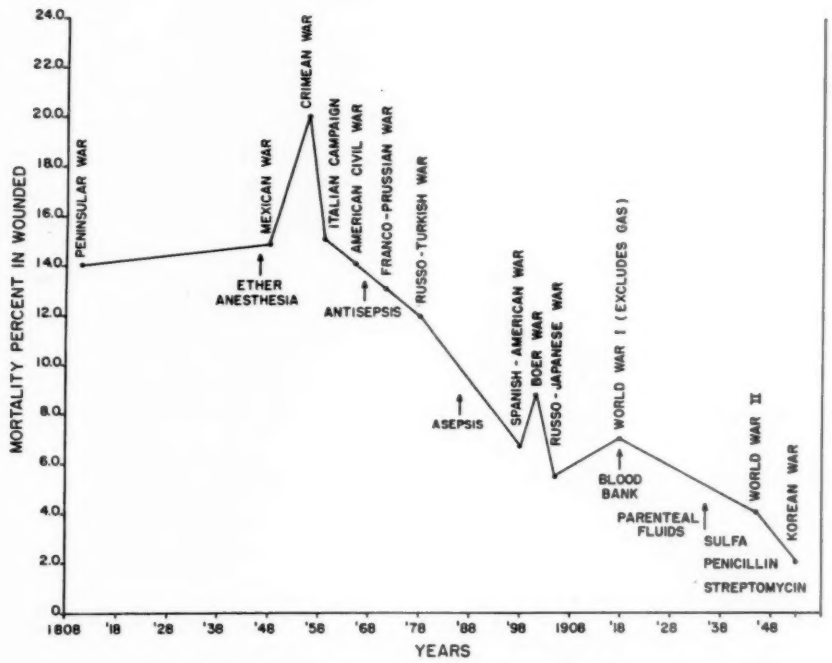

Fig. 2.—Percentage of injured dying of wounds in various wars.

Lister came to America in 1876 and spoke at the Medical Congress in connection with the Philadelphia Centennial Exposition.[13] He spoke for 2½ hours. It is said that he impressed his audience with the germ theory of wound infections. The treatment was certainly immediately taken up by many surgeons throughout the country, but it was apparently poorly understood, as is evidenced by the discussion of a paper by Watson given at the meeting of the American Surgical Association which was held in 1883. Watson heartily endorsed Lister's treatment and reminded his fellow members that it was Francisco Redi who in 1668 "was the first to give utterance to this remarkable hypothesis, '*no life without antecedent life*,'" and that the work of Pasteur and others " . . . (has) effectually succeeded in banishing the notion of spontaneous generation; and (has) likewise shown that fermentation and putrefaction

can only be produced by living germs.''[22] Not all of Dr. Watson's colleagues were quite so convinced. Dr. Packard of Philadelphia, Dr. Post of New York, Dr. Vanderveer of Albany, and several others immediately rose to denounce the treatment and to declare that it has been abandoned in their own communities. There was apparently no real appreciation of the meaning of what Lister was trying to promote. As noted by one writer of the times, this included: ''Equable temperature, absolute immobility, continuous pressure, and thorough drainage, which either alone or in combination tend to moderate and control inflammation in wounds . . . Lister, however, insists upon the importance of carbolic acid . . .''[4] David Prince of Jacksonville, Illinois stated the case fairly: ''If Listerism means the detail of the dressing of wounds, doubtless it is short lived, but if Listerism means the *principles* which are involved in antisepsis, Listerism is immortal.''[20]

So with the attitudes toward Lister somewhat skeptical, there might well have been some delay in Philadelphia in the enthusiastic adoption of antiseptic principles. Even after antisepsis and asepsis were well established, Francis Packard related how difficult it was for some of the older surgeons to mend their ways. One famous ophthalmologist had an unbreakable habit of holding his scalpel handle in his teeth when operating, with the blade protruding through one side of his bushy whiskers and the end of the handle through the other side.[17]

Since we are interested in delving into what Erichsen calls the ''surgical salubrity''[11] of the hospital in pre-Listerian days, we have, like Erichsen, Simpson, Morton, Norris, and others, taken major amputations as the ''test-operation.'' We realize, as Erichsen has said, that there are many variables in the operations for amputations that may be resolved only by analyzing very large numbers of cases. The importance of these variables is magnified when comparisons are attempted over a span of 100 years. With more emphasis on the historic aspects of this presentation than on the scientific, we have attempted to make some comparisons between amputation of the thigh and leg performed 100 years ago at Lister's hospital, the Royal Infirmary of Glasgow, and the New Haven Hospital 100 years later during the period of 1944 through 1953 (Fig. 3).

As to the reason for amputations, in Lister's day injury was the indication for 73 per cent of the amputations. It was Charriere in 1692 who is credited, by Thomson's writing in 1816, to have been the first to suggest amputation in the presence of trauma and without mortification.[21] This suggestion followed the introduction of the ligature by Paré. So frequent did amputation become in the French Army that Louis XIV ''Conceived the injured limbs of his soldiers to have been fully as much in danger from the chirurgical ardour of the assistant surgeons, as their lives had ever been from the fire of the enemy.'' To this charge the senior surgeon, Dionis, replied that ''il vaut mieux vivre avec trois extremitiés que mourir avec quatre.''[21]

With trauma being the most frequent indications for amputations in the nineteenth century, one might expect the male sex to be more frequently involved. In the twentieth century the average age at the time of amputation

had advanced nearly 40 years, and disease rather than trauma was more frequently the cause for amputation. The woman thus came to take more of her share of this operative procedure. Amputation below rather than above the knee was more frequently performed in the twentieth century. There were several factors involved in the lowering of the level of amputation in modern times, but certainly the more distal amputation is to be preferred (Fig. 3).

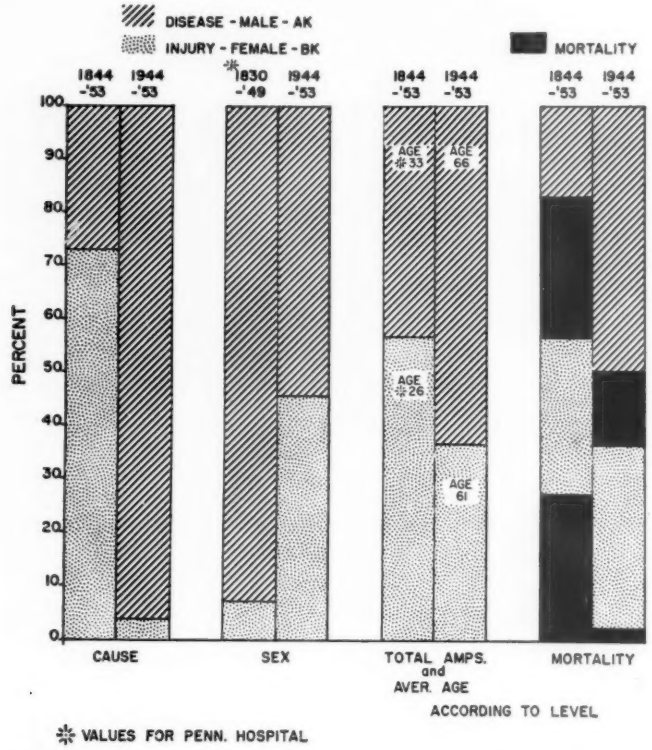

Fig. 3.—A comparison of amputations of thigh and leg for 10-year periods 100 years apart. Glasgow Royal Infirmary (1844-1853) 167 amputations; New Haven Hospital (1944-1953) 344 amputations.

The decrease in mortality following amputations of the lower extremity from the time just prior to Lister to the present is quite obvious. It is particularly remarkable when one considers the advanced age and cause for amputation in most of the amputations performed in the twentieth century. It is not intended to imply that the development of antisepsis and asepsis was wholly responsible for the improvement in mortality in amputations from injury, disease, and lesions between the nineteenth and twentieth centuries. But one cannot deny the significance of the immediate acceptance of the germ theory of Pasteur by Lister and its application to the surgical problem—indeed to the problem of amputation, as compound fractures were so often in need of amputation due to almost inevitable sepsis. Despite the advance in years and the increasing emphasis on disease as a cause for amputation, the mortality is remarkably different for the two periods. In the 1840's it was about 60 per cent for the thigh amputations as compared with 16 per cent in the 1940's,

while the leg amputations showed 46 per cent mortality in the 1840's and only 6.5 per cent in the 1940's. In summary, one of the fairer sex may have mixed feelings when viewing this chart. She might well say that she now has a chance to live long enough to lose her leg, but if this is some comfort, it will probably come off below the knee, and she will probably survive, at least for a while!

There is another way to view the surgery of the times. It seems that from time to time some tormented or deranged mind rises up to protest, by violent and brutal action, a just or unjust grievance. Three of our presidents have suffered assassination while in office. We have drawn on the history of the lives of certain notables where the treatment given reflected the best available at that time.[3, 21] With the exception of Lincoln, who could probably not have been spared irreparable damage under any circumstances, the remaining notable persons might have been saved with the same care given recently to Representative Bentley.[3] His injury was the most severe save that suffered by Lincoln, yet because of the skill and modern training of his surgeons and the prompt and modern care given him, he survived. The use of a motor-driven sump placed in the depths of the abdominal wound close to a severely lacerated liver and the use of repeated thoracentesis in the treatment of the wounded lung undoubtedly contributed to his recovery (Table I).

TABLE I. EVOLUTION OF SURGICAL TREATMENT IN NOTABLE AMERICANS OVER A 90-YEAR PERIOD (1865-1954)

DATE	NAME	INJURY	TREATMENT	RESULT
1865	Lincoln	Brain (bullet)	1. Probing of wound	Died (extensive brain damage)
1881	Garfield	Abdomen (bullet)	1. Probing of wound	Died (ruptured aneurysm of splenic artery)
1901	McKinley	Abdomen (bullet)	1. Laparotomy (suture of stomach	Died (shock? pancreatitis)
1935	Long	Abdomen (bullet)	1. Laparotomy (suture of colon) 2. Transfusions	Died (retroperitoneal hemorrhage)
1954	Bentley	Chest, abdomen (bullet)	1. Laparotomy (suture of stomach) 2. Transfusions 3. Antibiotics	Recovered

The aseptic technique that typifies the modern operating room has arrived with painful slowness. Its progress is illustrated by a remarkable series of photographs and portraits of noted clinics.[5] At the turn of the century, a brief 50 years ago, rubber gloves had just been introduced by Halstead in Baltimore as Harvey Cushing assisted him across the table (Fig. 4). The use of chemotherapy, blood banks, parenteral therapy, gastric and intestinal suction, and masks to cover the nose and mouth had not begun. But even this was ahead of Agnew at the University of Pennsylvania only 10 short years before, who covered with a gown but without gloves or cap, could only begin to envision the realization of aseptic needs (Fig. 5). And then but 20 years before

Fig. 4.—At the turn of the century, a brief 50 years ago, rubber gloves had just been introduced by Halstead in Baltimore as Harvey Cushing assisted him across the table.

Fig. 5.—Agnew, only 10 years before Halstead introduced rubber gloves, covered with a gown but without gloves or cap.

Agnew was Gross in 1870 in his clinic at Jefferson, represented by what is probably one of the most outstanding portraits ever done by an American artist (Fig. 6). And well might such a splendid effort immortalize the struggle of this man against infection. He stood astride the septic era, with one foot mired in pus and the other just beginning to reach for higher (and drier) ground.

Fig. 6.—Portrait of Gross in 1870 in his clinic at Jefferson Medical College of Philadelphia.

One might dispute the assertion that the development of antisepsis and aseptic techniques have per se contributed significantly to the more than six-fold increase in the population of the United States over the past 100 years or to the extension of the life span from about 50 years in 1900 to about 70 years in 1955. However, at the least, the advances in medicine and surgery have established confidence in the public health services, the hospitals, and the physicians and there is little doubt that these developments have been enhanced by the cleaner atmosphere of the aseptic era. The social impact of curative medicine and surgery has been to establish the faith of the people in the hospital as a House of Hope rather than a House of Pity.[6]

I am indebted to Dr. J. W. Braden for the privilege of reporting the care given Representative Bentley.

I am grateful to the following institutions for the privilege of reproducing: Fig. 4, The Historical Library, Yale University, School of Medicine; Fig. 5, The Jefferson Medical College of Philadelphia; Fig. 6, The University of Pennsylvania.

I am grateful also to the Pennsylvania Hospital for permission to obtain the data included in Figs. 1 and 3.

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Book Reviews

CONDUCTED BY J. GARROTT ALLEN, M. D.

Anatomies of Pain. H. D. Keele. Springfield, Ill., 1957, Charles C Thomas. $5.50.

There is little in this book that would be of direct value to a physician or surgeon in the diagnosis and treatment of pain syndromes but this is not its purpose. There is here, in less than 200 pages, a most remarkable survey of the history of ideas concerning the nature of pain and its anatomic and physiologic basis. The story begins with the pre-eminence of the heart as the seat of all sensory experience in the ancient Egyptian, Mesopotamian, and Indian civilizations and traces this cardiovascular anatomy of sensation to its culmination in Aristotle, whose powerful influence on biologic thought has persisted even to the present time (in the ideas of René Leriche, for example) in spite of the subsequent establishment of the nervous system as the organ of sensory-motor functions by the Alexandrian School and by Galen.

The working out of the classical modalities of sensation and their pathways in the central nervous system is traced in the observations of the anatomists, physiologists, and clinicians of the nineteenth and early twentieth centuries. Finally, there is a brilliantly complete, yet succinct, account of the current realization of the inadequacy of rigid anatomic patterns to account for the great variety of sensory phenomena in general and pain in particular. Biochemical factors and the activity of the autonomic nervous system and the brain stem reticular system are a few of the areas in which the physical correlates of complex pain phenomena are to be found. The insights of the ancients were not closely approached by the discovery of the classical sensory pathways, nor are they yet, by any means, completely fitted out in physiologic and anatomic raiment.

This book is highly recommended for those who enjoy that species of clarification which comes with historical perspective.

—Sidney Schulman

Suprapubic Closure of Vesicovaginal Fistula. Vincent J. O'Conor. Springfield, Ill., 1957, Charles C Thomas. $2.50.

This monograph deals with the management of urinary tract fistulas in the woman.

It is pointed out that gynecologic surgery has supplanted obstetric trauma as the major cause of vesicovaginal fistulas and that these fistulas resulting from pelvic surgery tend to be high-lying and, hence, are frequently more difficult to repair by the vaginal route than the low-lying fistulas resulting from obstetric injury.

The author believes that the suprapubic repair of vesicovaginal fistulas is the procedure of choice in those instances where careful evaluation indicates that vaginal closure cannot easily be accomplished because of the location of the fistulas or because of scarring as a result of previous unsuccessful attempts at vaginal closure.

The technique for the excision and closure of high-lying vesicovaginal fistulas by the extraperitoneal bisection of the bladder wall which has been developed by the author and by which he has achieved primary closure in 33 of 35 complicated vesicovaginal fistulas is presented.

The value of this monograph is enhanced by a series of excellent illustrations depicting the operative procedures, by detailed discussion of preoperative evaluation and postoperative management of these patients, and by the inclusion of case histories.

This authoritative monograph is a significant contribution to current medical literature.

—Charles P. McCartney

Handbook of Orthopedic Surgery. Alfred Reves Shands, Jr., with Richard Beverly Roney. St. Louis, Mo., 1957, The C. V. Mosby Company. Ed. 5. Pp. 630. $9.75.

This compendium of orthopedic diseases, designed specifically for students and general practitioners, is now in its fifth edition. Included in this volume are new sections dealing with rehabilitation, Fanconi's syndrome, Letterer-Siwe's disease, Gaucher's disease, osteopathia striata, Caffey's disease, osteitis pubis, Guillain-Barre's syndrome, nonosteogenic fibroma, chondromalacia patellae, hallux varus, cervical root syndrome, bicipital tenosynovitis, frozen shoulder, and shoulder-hand syndrome. Of these, the discussion of the painful, stiff shoulder is especially interesting. The remainder of the book has been revised.

The book attempts to cover the entire field of orthopedic surgery from congenital anomalies to the degenerative diseases, excluding acute fracture management. It also includes a few sections on nervous system diseases. In doing so, the authors are very concise and stress only principles of diagnosis and therapy. It is the necessary brevity which may lend to some of the drawbacks of this presentation.

With these objections in mind, it is felt that this book also should be valuable to the student and resident in orthopedics who will find the extensive bibliography which is included to be very useful as a convenient source of reference material from which he can expand his scope of reading material.

—Jason A. Appel

Closed Treatment of Common Fractures. John Charmley. Baltimore, Md., Williams & Wilkins Company.

As the title would suggest, *Closed Treatment of Common Fractures* is not purported by the author to be a comprehensive textbook on the subject of traumatic injuries to bones and joints. Rather, it is a monograph written with a view to restimulate interest in the nonoperative management of fractures emphasizing the undesirable factors associated with the operative treatment of fracture.

Mr. Charmley believes that the surgical approach to fractures today is taken altogether too lightly, especially in America, and that the acceptance of methods of internal fixation has been without critical thought or a full understanding of the true nature of bone healing. He points out that the successful conservative management of a fracture is often more time-consuming and requires more inherent skill and judgment than the operative management of the same fracture. His advocacy of the closed method is based upon biologic concepts which may or may not be valid, namely, that open reductions adversely affect the normal healing process of bone. A thorough understanding of bone physiology, a clear mental picture of the pathology of fractures, and the proper application of sound mechanical principles in effecting a closed reduction together constitute the premises upon which the author builds his case in favor of the closed method of treating fractures.

The first six chapters are devoted to the nature of fracture repair, the inhibiting effect of surgical trauma upon healing, the mechanics of closed reduction, the importance of proper plaster technique, and a discussion of joint movement in the conservative management of fractures. The chapter on joints, although short, is particularly enlightening and offers useful information regarding the etiology and preservation of that all too common complication of fractures, the stiff joint. The remaining chapters, ten in all, cover in customary fashion the more commonly occurring fractures with reference to

specific locations. In each case, emphasis is placed upon the importance of a clear understanding of the mechanics involved and the necessity of carrying out specific manipulative steps in effecting a successful closed reduction.

The author's style is clear and concise. There is some repetition of certain basic principles, but this is not objectionable since it serves to fix the more important facts in the reader's mind. The text is admirably complemented by line drawings which clearly illustrate the reading matter.

Although many experienced orthopedic surgeons may not share Mr. Charmley's enthusiasm for the closed method of fracture treatment in all cases, notably in depressed fractures of the tibial plateau and fractures of the adult femoral shaft, few, it is felt, will deny the merits of his book as a clear, practical guide to the mechanics of closed reduction of fractures. This book should prove of particular interest and usefulness to the neophyte orthopedist and as source material for reference for those who are more experienced.

—Frederick N. Reed

Degenerative Changes in the Sternoclavicular and Acromioclavicular Joints in Various Decades. Anthony F. DePalma. Springfield, Ill., 1957, Charles C Thomas. Pp. 178. $5.50.

The author is concerned with analyzing the degenerative changes which occur in the sternoclavicular and acromioclavicular joints with aging. For this purpose he has assembled 223 sets of sternoclavicular and acromioclavicular joints from autopsy specimens ranging in age from prematurity to senescence. By employing gross and microscopic observation as well as roentgenographic and photographic methods, the author has determined that these joints undergo the same degenerations as all other major joints of the body.

The author has correlated the degeneration of the fibrocartilaginous disks in both the acromioclavicular and sternoclavicular joints with the subsequent degeneration of these joints, and he concludes that the integrity of the joint is dependent upon the intact disk.

The book provides some new and original information, but it serves best to round out a subject upon which relatively little has been written. The author has been extremely thorough in this investigation and the text is abundantly documented with photographs and photomicrographs. The text is wordy, at times ambiguous and confusing.

—Joel B. Dennis

Clinical Gastroenterology. Eddy D. Palmer. New York, 1957, Paul B. Hoeber, Inc. Pp. 630. $18.50.

This is a presentation of gastroenterology in which the author covers the subject as he believes it to be from the standpoint of the practicing physician. The subject matter includes the alimentary tube from the tongue to the anus, as well as its embryologic appendages, the liver and pancreas, and also the spleen.

In his approach to this subject, the author pursues one with little concern for the views that may differ from those he presents. This is excusable, since he states these and other limitations in his preface, where he details his reasons for the obvious omissions of many current and past references to the physiology of gastroenterology. Many, however, believe physiology to be the one discipline in this field which has enabled the clinical gastroenterologist to advance his diagnostic and therapeutic measures beyond those used in the days of Walter Cannon and of Bertram Sippy 40 years ago. Instead, eponymic atavism is employed with little desire or attempt to use the more recent nomenclatures of the pathologist and physiologist to which most clinical surgeons of today have become accustomed. Clinical impressions dominate the more frequently employed methods others generally have used in the documentation of the bedside conclusions presented here.

The author expresses his views clearly, despite their rather unusual character. For example, from page 160 is the following quotation relative to the surgical treatment of carcinoma of the stomach: "There is serious question whether most patients with cancer of the stomach are helped more than they are hurt when current methods are utilized in an effort to cure them."

If the reader is willing to concede his rights to the author on such items as the use of minimal bibliographic material and the omission of discussions on experimental gastroenterology in favor of clinical conclusions and agrees that "it is permissible to define gastroenterologic disease only in terms of its effect upon the patient, not in terms of its appearance to the pathologist," then he will find little to criticize in this book.

—J. Garrott Allen

Calendar of Surgical Meetings

AMERICAN ASSOCIATION OF GENITO-URINARY SURGEONS. *Annual Meeting,* April 23-25, 1958, Edgewater Gulf Hotel, Edgewater Park, Miss. Secretary-Treasurer, Dr. Wm. J. Engel, 2020 East 93rd Street, Cleveland, Ohio.

THE AMERICAN ASSOCIATION FOR THORACIC SURGERY. *Annual Meeting,* May 16-18, 1958, Statler Hotel, Boston, Mass. Secretary, Dr. H. T. Langston, 1919 West Taylor Street, Chicago 12, Ill.

AMERICAN GYNECOLOGICAL SOCIETY. *Annual Meeting,* May 19-21, 1958, The Grove Park, Asheville, N. C. Secretary, Dr. Andrew A. Marchetti, Georgetown University Hospital, Washington 7, D. C.

AMERICAN SURGICAL ASSOCIATION. *Annual Meeting,* April 16-18, 1958, Waldorf-Astoria, New York, N. Y. Secretary, Dr. William A. Altemeier, Cincinnati General Hospital, Cincinnati, Ohio.

AMERICAN UROLOGICAL ASSOCIATION. *Annual Meeting,* April 28—May 1, 1958, Roosevelt Hotel, New Orleans, La. Secretary, Dr. Samuel L. Raines, 188 South Bellevue Boulevard, Memphis 4, Tenn.

THE HARVEY CUSHING SOCIETY. *Annual Meeting,* April 21-23, 1958, The Mayflower, Washington, D. C. Secretary, Dr. David L. Reeves, 316 West Junipero Street, Santa Barbara, Calif.

THE INTERNATIONAL CARDIOVASCULAR SOCIETY. *North American Chapter,* June 21, 1958, Sir Francis Drake Hotel, San Francisco, Calif. Secretary, Dr. Henry Haimovici, 105 East 90th Street, New York 28, N. Y.

INTERNATIONAL UNION AGAINST CANCER. *Seventh International Cancer Congress,* July 6-12, 1958, London, England. Secretary General, Harold Dorn, National Institute of Health, Bethesda 14, Md.

NEW ENGLAND SURGICAL SOCIETY. *Annual Meeting,* Oct. 3 and 4, 1958, Mount Washington Hotel, Burton Woods, N. H. Deadline for submission of papers, June 1, 1958. Secretary, Dr. Richard Warren, Peter Bent Brigham Hospital, 721 Huntington Avenue, Boston 15, Mass.

WESTERN SURGICAL ASSOCIATION. *Annual Meeting,* Nov. 20-22, 1958, Hotel Kahler, Rochester, Minn. Deadline for submission of papers, Sept. 1, 1958. Secretary, John T. Reynolds, M.D., 612 N. Michigan Ave., Chicago 11, Ill.